Ted K. Ringsred
Intellectual Property Counsel

Office of Intellectual
Property Counsel

#12

3M

April 2, 1997

Honorable Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Included herewith is an Application for Patent Extension (Attorney's Docket No. F.N. 43682USA5C) of the term of U.S. Patent No. 5,238,944 being filed by Riker Laboratories, Inc. Please charge the filing fee of $1090.00 to Deposit Account No. 13-3723. Please charge to Deposit Account No. 13-3723 any additional fees under 37 CFR 1.16 and 1.17 which may be required during the entire pendency of this application. This authorization includes the fee for any extension of time under 37 CFR 1.136(a) that may be necessary. To the extent any such extension should become necessary it is hereby requested.

Respectfully submitted,

Ted Ringsred

Ted K. Ringsred
Registration No. 35,658

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p:\feulngre\pte\imiquimod\patexten.ltr

Minnesota Mining and
Manufacturing Company

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St. Paul, MN 55133-3427 USA
612 736 5839
612 736 3833 Facsimile
29 7023 Telex
PATENTS Cable

PATENT
Docket No. 43682USA5C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 5,238,944

APPLICATION FOR PATENT EXTENSION

Honorable Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

Applicant, Riker Laboratories, Inc., hereby applies for extension of the term of U. S. Patent No. 5,238,944. A power of attorney in favor of the undersigned is submitted herewith.

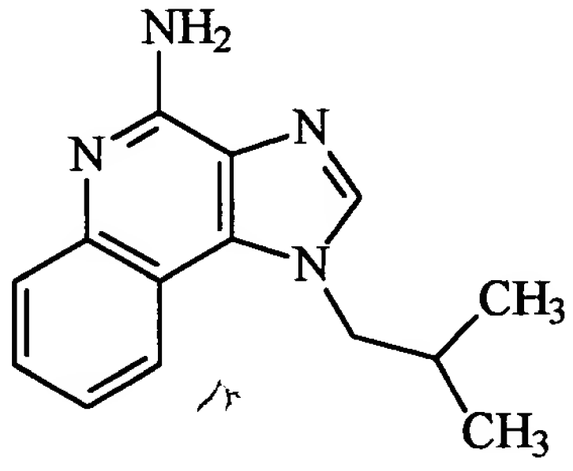
BACKGROUND

This application for patent extension concerns U.S. Patent No. 5,238,944. Riker Laboratories, Inc. is the owner of U.S. Patent No. 5,238,944 , the written assignment being recorded on November 30, 1989, and found at Reel 5187, Frame 990. The 3M Pharmaceuticals division of the Minnesota Mining and Manufacturing Company (3M) has applied for and obtained Food and Drug Administration (FDA) approval for the commercial marketing of ALDARA™ (imiquimod) 5% cream on February 27, 1997. Imiquimod is claimed in U.S. Patent No. 4,689,338 and U.S. Patent No. 5,238,944. In addition to the present application, Riker Laboratories, Inc. has concurrently submitted an application for patent term extension of Patent No. 4,689,338. Riker Laboratories, Inc. will choose to extend the term of only one patent if granted the opportunity to extend both patents.

APPLICATION (37 CFR 1.740(a))

(1) The tradename for the product approved by the FDA is ALDARA™ (imiquimod) 5% cream. The active ingredient of ALDARA™ is imiquimod. Chemically, imiquimod is 1-(2-

methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine, and the compound has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3. Its structural formula is:



A copy of an approved package insert for ALDARA™ (imiquimod) 5% cream, wherein all sections thereof are reproduced on several pages, is attached hereto as Exhibit A. The package insert further describes the approved product.

(2) The Federal statute under which the regulatory review occurred for the active ingredient imiquimod is § 505(b) of the Food, Drug and Cosmetic Act (21 U.S.C. § 355(b)).

(3) Imiquimod, presented as Aldara™ 5% cream, was approved by the FDA under § 505(b) of the Federal Food, Drug and Cosmetic Act on February 27, 1997, for commercial marketing and use as a drug product for the treatment of external genital and perianal warts/condyloma acuminata in adults.

(4) As mentioned, the active ingredient of ALDARA™ (imiquimod) 5% cream is imiquimod. Imiquimod has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application for patent extension is being submitted within the sixty day period permitted for submission as provided in 35 U.S.C. § 156(d)(1) or 37 C.F.R. § 1.720(f), the last day on which the application could be submitted being April 27, 1997.

(6) The subject of this application for patent extension is U.S. Patent No. 5,238,944 which issued on August 24, 1993, and expires on August 24, 2010. The inventors named in this patent are Steven M. Wick, Helen J. Schultz, Gregory R. Nelson, Amit K. Mitra, and Stephen M. Berge. The assignee of the patent is Riker Laboratories, Inc., located in St. Paul, Minnesota. U.S. Patent No. 5,238,944 issued on a continuation of Serial Number 444,555, now abandoned, which is a continuation-in-part of Serial Number 284,933, now abandoned. U.S. Patent No. 5,238,944 has not been previously extended or the subject of an application for patent extension.

(7) A copy of U.S. Patent No. 5,238,944 is attached hereto as Exhibit B.

(8) The patent is free of any disclaimers and reexamination certificates. One certificate of correction and a receipt of maintenance fee payment have issued on the patent and are attached hereto as Exhibit C.

(9) Claims 1 through 13 of U.S. Patent No. 5,238,944 read on the approved product imiquimod (1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine). The chemical 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine is equivalent to 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine.

CLAIM #	MANNER OF CLAIMING THE APPROVED PRODUCT
1	Claims a pharmaceutical composition comprising 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine for topical and/or transdermal administration.
2	Claim 2 is dependent on claim 1 and claims a pharmaceutical composition comprising 1-isobutyl-1H-imidazo[4,5-c] quinoline-4-amine in an amount of about 0.5 percent to about 9 percent by weight based on the total weight of the composition.
3	Claim 3 is dependent on claim 1 and claims a pharmaceutical composition comprising 1-isobutyl-1H-imidazo [4,5-c] quinoline-4-amine in the form of a cream.
4	Claim 4 is dependent on claim 3 and claims a pharmaceutical composition comprising 1-isobutyl-1H-imidazo[4,5-c] quinoline-4-amine in a cream wherein isostearic acid is present in an amount of about 5 percent to about 25 percent by weight based on the total weight of the composition.
5	Claim 5 is dependent on claim 1 and claims a pharmaceutical composition comprising 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in the form of an ointment.
6	Claim 6 is dependent on claim 3 and claims a pharmaceutical composition comprising 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in an amount of about 1 percent to about 5 percent by weight based on the total weight of the composition, the composition in the form of a cream.
7	Claim 7 is dependent on claim 4 and claims a pharmaceutical composition comprising about 1 percent of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, the composition in the form of a cream.
8	Claim 8 is dependent on claim 4 and claims a pharmaceutical composition comprising 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in the form of a cream.
9	Claim 9 is dependent on claim 4 and claims a pharmaceutical composition comprising 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in the form of a cream.
10	Claim 10 is dependent on claim 4 and claims a pharmaceutical composition comprising 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in the form of a cream.
11	Claim 11 is dependent on claim 4 and claims a pharmaceutical composition comprising 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in the form of a cream.
12	Claims a method of using 1-isobutyl -1H-imidazo[4,5-c]quinolin-4-amine for treatment of viral disease in a mammal.
13	Claims a method of using 1-isobutyl -1H-imidazo[4,5-c]quinolin-4-amine to induce interferon biosynthesis in a mammal.

(10) An Investigational New Drug application (IND) for ALDARA™ (imiquimod) 5% cream was submitted to the Food and Drug Administration (FDA) on July 30, 1987. The IND (# 30,432) was recorded in the FDA on July 31, 1987, as an exemption under subsection (i) of § 505 of the Food, Drug and Cosmetic Act (21 U.S.C. § 355 (i)) and the exemption became effective on September 1, 1987. A New Drug Application (NDA, #20-723) on ALDARA™ (imiquimod) 5% cream was filed by 3M Pharmaceuticals under § 505 (b) of the Food, Drug and Cosmetic Act (21 U.S.C. § 355 (b)) on July 25, 1996. The NDA was approved on February 27, 1997.

(11) A brief description of activities undertaken by the Applicant during the regulatory review period of imiquimod and the significant dates applicable to such activities are as follows:

An acute oral toxicity study in mice (#1183AM0363) was conducted from August 16, 1983, through September 22, 1983. The report was issued on November 18, 1983.

An acute intraperitoneal toxicity study with mice (#1183AM0364) was conducted from August 16, 1983, through October 5, 1983. The report was issued on December 29, 1983.

A primary skin irritation test in rabbits (#0983EB0510) was conducted from November 1, 1983, through November 4, 1983. The report was issued December 27, 1983.

An acute oral toxicity study in rats (#0983AR0505) was conducted from November 17, 1983, through December 6, 1983. The report was issued on January 24, 1984.

An acute dermal toxicity study in albino rabbits (#0983AB0504) was conducted from November 18, 1983, through December 2, 1983. The report was issued January 24, 1984.

A ten-day dose rangefinding toxicity study in rats (#0284RR0432) was conducted from August 6, 1984, through August 29, 1984. The report was issued on August 4, 1985.

A sensitization study in guinea pigs (#0984MG0528) was conducted from October 25, 1984, through December 8, 1984. The report was issued on February 3, 1985.

An acute ocular irritation test in rabbits (#0984EB0530) was conducted from October 29, 1984, through November 5, 1984. The report was issued on November 8, 1984.

An acute intraperitoneal toxicity study in rats (#0984AR0531) was conducted from November 7, 1984, through December 4, 1984. The report was issued on January 30, 1985.

A Salmonella/Mammalian-Microsome plate incorporation Mutagenicity (Ames test) study (#0784UK0547) was conducted from November 7, 1984, through January 25, 1985. The report was issued on January 25, 1985.

A twenty-eight day oral toxicity study in rats (#0284SR0642) was conducted from January 23, 1985, through February 20, 1985. The report was issued on May 15, 1987.

A twenty-eight day oral toxicity study in rats (#0285SR0450) was conducted from November 5, 1985, through January 1986. The report was issued on February 27, 1987.

An acute ocular irritation test in rabbits (#0985EB0499) was conducted from November 19, 1985, through November 26, 1985. The report was issued on January 16, 1986.

A study of the maximum tolerated dose administered intravenously to Cynomolgus monkeys (#0786AP0149) was conducted from April 22, 1986, through April 28, 1986. The report was issued on February 20, 1987.

A Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity (Ames test) study (#0786UK0272) was conducted from June 17, 1986, through August 7, 1986. The report was issued on August 7, 1986.

An L5178Y $TK^{+}/-$ Mouse Lymphoma Mutagenesis study (#0786UK0270) was conducted from June 18, 1986, through July 31, 1986. The report was issued on August 1, 1986.

A chromosome aberration study in Chinese Hamster ovary cells (#0786UK0268) was conducted from June 18, 1986, through September 10, 1986. The report was issued on September 10, 1986.

A subchronic *in vivo* cytogenetics assay in male and female rats (#0786UR0273) was conducted from June 24, 1986, through September 29, 1986. The report was issued on September 29, 1986.

A study of dominant lethal mutations in mice (#0786UK0271) was conducted from June 24, 1986, through October 29, 1986. The report was issued on October 29, 1986.

A subchronic *in vivo* cytogenetics study in male and female hamsters (#0786UH0274) was conducted from June 25, 1986, through October 29, 1986. The report was issued on October 29, 1986.

A study of chromosome aberration in human lymphocytes (#0786UK0269) was conducted from July 1, 1986, through September 24, 1986. The report was issued on September 24, 1986.

A maximum tolerated intravenous (bolus) dose study in Rhesus monkeys (#0786AP0415) was conducted from September 25, 1986, through October 30, 1986. The report was issued on March 5, 1987.

The IND was submitted on July 30, 1987.

The stated date of receipt by the FDA was July 31, 1987, and IND # 30,432 was assigned.

The FDA granted permission to proceed with the first clinical study as described in the IND on September 1, 1987.

Clinical study R-837T-001 was initiated on October 5, 1987, and conducted through May 1988. The clinical report was issued in April 1990.

An acute subcutaneous toxicity study in rats (#1187AR0410) was conducted from November 2, 1987, through November 17, 1987. The report was issued on June 9, 1988.

An acute oral toxicity study in Cynomolgus monkeys (#0787AP0438) was conducted from February 1, 1988, through March 8, 1988. The report was issued on September 27, 1988.

A dosage range developmental toxicity study with intravenous administration in rabbits (#0788RB0276) was conducted from July 23, 1988, through September 9, 1988. The report was issued on September 16, 1988.

A dosage range developmental toxicity study with administration by gavage to pregnant rats (#0788RR0274) was conducted from July 27, 1988, through September 16, 1988. The report was issued on October 7, 1988.

A twenty-eight day oral toxicity study in Cynomolgus monkeys (#0788SP0130) was conducted from July 1988, through January 1989. The report was issued on September 28, 1989.

A primary skin irritation test in rabbits (#1188EB0367) was conducted from August 30, 1988, through September 2, 1988. The report was issued on January 18, 1989.

A sensitization study in guinea pigs (#1188MG0368) was conducted from September 6, 1988, through September 30, 1988. The report was issued on January 12, 1989.

A developmental toxicity with administration by gavage to pregnant rats (#0788TR0275) was conducted from November 15, 1988, through December 22, 1988. The report was issued on June 2, 1989.

A developmental toxicity study with intravenous administration in rabbits (#0788TB0277) was conducted between November, 1988 and December, 1988. The report was issued on June 2, 1989.

Clinical study R-837T-003 was conducted between January and February, 1989. The report was issued in January, 1991.

A twenty-six week oral toxicity study in rats (#0189SR0036) was conducted from March 4, 1989, through September 3, 1989. The report was issued on August 20, 1990.

Clinical study R-837T-004 was conducted between May, 1989, and July, 1990. The report was issued on October 25, 1991.

Clinical study R-837T-005 was conducted between June, 1989, and April, 1990. The report was issued on October 25, 1991.

Clinical study R-837T-008 was conducted from July 28,1989, through September 19, 1989. The report was issued in January, 1992.

A 26-week oral toxicity study in Cynomolgus monkeys (#0788SP0131) was conducted from August 1, 1989, through November, 1990. The report was issued on November 28, 1990.

An eight-week oral toxicity study in Cynomolgus monkeys utilizing twice-a-week dosing (#0790SP0074) was conducted from April 23, 1990, through June 15, 1990. The report was issued on December 20, 1990.

A twelve-week oral toxicity study in rats using alternate dose schedules (#0290SR0308) was conducted from September 4, 1990, through December 5, 1990. The report was issued on January 30, 1992.

A fertility and general reproduction study in rats (#0790GR0318) was conducted from September 26, 1990, through June 4, 1991. The report was issued on November 20, 1991.

Clinical study R837T-017 was conducted between April, 1991, and April, 1992. The report was issued on April 30, 1992.

A bone marrow and lymphoid organ study in orally dosed rats (#0191MR0293) was conducted from August 7, 1991, through October 29, 1991. The report was issued on December 30, 1992.

An acute dermal toxicity test in rabbits (#0791AB0424) was conducted from December 3, 1991, through December 18, 1991. The report was issued March 1992.

A pilot dermal rat toxicity study (#0892SR0160) was conducted from April 22, 1992, through May 19, 1992. The report was issued on April 29, 1993.

An End of Phase II Meeting with FDA was held on May 4, 1992.

An in vitro transformation study using Syrian Golden Hamster cells (#0792UK0326) was conducted from July 30, 1992, through November 25, 1992. The report was issued on February 26, 1993.

Clinical study 1004-IMIQ was conducted between September, 1992, and May, 1994. The report was issued on December 1, 1994.

Clinical study 1005-IMIQ was conducted between September, 1992, through July, 1994. The report was issued on February 16, 1995.

A three-week pilot dermal mouse toxicity study (#0892RM0389) was conducted from September 14, 1992, through October 5, 1992. The report was issued on June 3, 1993.

A four-month dermal study in rats (#0792SR0306) was conducted from September 18, 1992, through June 8, 1993. The report was issued on October 22, 1993.

A six-month oral rangefinder study in young and old rats (#0292RR0314) was conducted from October 6, 1992, through April 7, 1993. The report was issued on June 15, 1994.

A dermal rangefinder mouse toxicity study (#1192RM0472) was conducted from November 16, 1992, through March 12, 1993. The report was issued on August 5, 1993.

Clinical study 1027-IMIQ was conducted from February 1, 1993, through August 16, 1993. The report was issued on August 25, 1994.

Clinical study 1042-IMIQ was conducted from March 9, 1993, through August 17, 1993. The report was issued on March 11, 1994.

U.S. Patent No. 5,238,944 was issued August 24, 1993.

A meeting with FDA was held on September 22, 1993, to discuss the dermal carcinogenicity protocol and to present clinical data.

A ten-day repeat skin irritation test in rabbits (#0193EB0368) was conducted from October 5, 1993, through October 15, 1993. The report was issued on November 3, 1993.

A three-week pilot dermal mouse study (#0193AM0399) was conducted from November 8, 1993, through November 29, 1993. The report was issued on January 10, 1994.

Clinical study 1109-IMIQ was conducted between January, 1994, and February, 1995. The report was issued on August 2, 1995.

Clinical study 1110-IMIQ was conducted between February, 1994, and March, 1995. The report was issued on August 17, 1995.

A meeting with the FDA was held on February 28, 1994, to discuss chemistry and biopharmaceutics matters.

A thirteen-week mouse dermal rangefinder study (#1294RM0037) was conducted from March 2, 1994, through May 30, 1994. The report was issued on August 1, 1994.

An acute ocular irritation study in rabbits (#0494EB0192) was conducted from May 24, 1994, through May 27, 1994. The report was issued on Nov. 8, 1994.

Clinical study 1102-IMIQ was conducted from June 23, 1994, through August 12, 1994. The report was issued on December 22, 1994.

Clinical study 1103-IMIQ was conducted from August, 1994, through May 12, 1995. The report was issued on November 9, 1995.

A vaginal irritation study in rabbits (#0795EB0080) was conducted from March 1, 1995, through March 10, 1995. The report was issued on August 8, 1995.

Clinical study 1160-IMIQ was conducted from May 15, 1995, through June 5, 1995. The report was issued on November 7, 1995.

Clinical study 1161-IMIQ was conducted from June 26, 1995, through August 15, 1995. The report was issued on November 28, 1995.

A vaginal irritation study in rats (#1295ER0206) was conducted from June 6, 1995, through June 15, 1995. The report was issued on December 7, 1995.

A Pre-NDA Meeting with the FDA was held on July 10, 1995, for U-2h.

A ten-day repeat dose skin irritation/dermal toxicity study in rabbits (#1295EB0443) was conducted from October 17, 1995, through October 30, 1995. The report was issued on December 14, 1995.

Clinical study 1212-IMIQ was conducted from February 22, 1996, through May 10, 1996. The report was issued on May 31, 1996.

Clinical study 1213-IMIQ was conducted from January 15, 1996, through February 5, 1996. The report was issued on May 14, 1996.

A Pre-NDA meeting was held on February 5, 1996.

Clinical study 1214-IMIQ was conducted from February 14, 1996, through March 8, 1996. The report was issued on May 30, 1996.

The NDA Pre-Submission of the Chemistry, Manufacturing, and Controls Section was submitted on June 7, 1996.

The date of application for NDA 20-723 was July 25, 1996.

FDA acknowledgment of receipt of application was July 26, 1996.

A Post-Submission Meeting with 3M was held on August 26, 1996.

FDA issued an NDA Approval Letter on February 27, 1997.

(12) In the opinion of the applicant, U.S. Patent No. 5,238,944 is eligible for an extension of term. The extension claimed is 187 days as calculated herein, or a greater or lesser extension term as determined by the Commissioner under 35 U.S.C. § 156(g)(1) and 35 U.S.C. § 156(c). The length of the patent term extension was calculated under 37 C.F.R. § 1.775.

Patent Extension Calculation	**U.S. Patent 4,689,338**
Date IND became effective	September 1, 1987
Date NDA submitted to the FDA	July 25, 1996
Date NDA approved by the FDA	February 27, 1997
Patent issue date	August 24, 1993
U.S. Non-provisional Patent Filing Date	March 3, 1992
17 years from grant date	August 24, 2010
20 years from earliest effective U.S. filing date	December 15, 2008
Start date of regulator review period	September 1, 1987
IND review period (days) (starting from patent issue date)	1065
½ IND review period (days)	532
NDA review period (days)	217
NDA period + ½ IND period (days)	750
Expiration date of 5 year limitation period	August 24, 2015
Five year limitation period in days	1,826
Maximum Extension Period before 14 year limit	750
Expiration date before applying 14 year limit	September 12, 2012
Expiration of 14 years from NDA approval	February 27, 2011
Statutory Extension Period in days	**187**

(13) The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to this application for patent extension.

(14) Please charge the filing fee of $1090.00 to Deposit Account No. 13-3723. Please charge to Deposit Account No. 13-3723 any additional fees which may be required during the entire pendency of this application. This authorization includes the fee for any extension of time under 37 CFR 1.136(a) that may be necessary. To the extent any such extension should become necessary it is hereby requested. A declaration meeting the requirements of the guidelines is attached.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed to are:

Ted K. Ringsred
3M/Office of Intellectual Property Counsel
P.O. Box 33427
St. Paul, MN 55133-3427
(612) 736-5839

(16) A duplicate of the application papers, certified as such are attached hereto as Exhibit D.

(17) A signed declaration has been enclosed herewith identifying the papers and the patent for which an extension is being sought.

In view of the above, it is believed that U.S. Patent No. 5,238,944 is entitled to an extension of 187 days. An official notice to that effect in the form of a certificate of extension is courteously requested.

Respectfully submitted,

Ted K. Ringsred
Registration No. 35,658

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PTO/SB/ 96 (10/92)

CERTIFICATE UNDER 37 CFR 3.73(b)

Applicant: Steven M. Wick, Helen J. Schultz, Gregory R. Nelson, Amit K. Mitra and Stephen M. Berge

U.S. Patent No. 5,238,944, issued August 24, 1993

Application No.: 07/845,323 **Filed:** March 3, 1992

Entitled: TOPICAL FORMULATIONS AND TRANSDERMAL DELIVERY SYSTEMS CONTAINING 1-ISOBUTYL-1H-IMIDAZO[4,5-C]QUINOLIN-4-AMINE

Riker Laboratories, Inc., a corporation,

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application identified above. The assignment was recorded in the Patent and Trademark Office at Reel 5187, Frame 990, or for which a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application identified above, to the current assignee as shown below:

1. From:_____ To:_____
   The document was recorded in the Patent and Trademark Office at
   Reel _____, Frame _____, or for which a copy thereof is attached.

2. From:_____ To:_____
   The document was recorded in the Patent and Trademark Office at
   Reel _____, Frame _____, or for which a copy thereof is attached.

3. From:_____ To:_____
   The document was recorded in the Patent and Trademark Office at
   Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[X] Copies of assignments or other documents in the chain of title are attached.

The undersigned has reviewed all the documents in the chain of title of the patent application identified above and, to the best of undersigned's knowledge and belief, title is in the assignee identified above

The undersigned (whose title is supplied below) is empowered to sign this certificate on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

March 28, 1997
Date

Signature

Mark E. DuVal
Typed or printed name

Secretary
Title

Joint

ASSIGNMENT

Whereas we, Steven M. Wick, Helen Jensen Schultz, Gregory R. Nelson, Amit K. Mitra, and Stephen M. Berge citizens respectively of the United States of America, the United States of America, the United States of America, India, and the United States of America, residing respectively at the City of Mahtomedi, County of Washington, State of Minnesota, the City of Falcon Heights, County of Ramsey, State of Minnesota, the City of Hudson, County of St. Croix, State of Wisconsin, the City of Woodbury, County of Washington, State of Minnesota, and the City of Shoreview, County of Ramsey, State of Minnesota; have made an invention in

Topical Formulations and Transdermal Delivery Systems Containing
1-Isobutyl-1H-Imidazo[4.5-c]Quinolin-4-Amine (F.N. 43682 USA 7B)

and have today executed an application for Letters Patent of the United States of America based thereon:

Now, Therefore, for good and valuable consideration, receipt of which is acknowledged, we have individually and jointly agreed to assign and transfer and do hereby assign and transfer unto Riker Laboratories, Inc. a corporation organized on December 15, 1969, under the laws of the State of Delaware, United States of America, having offices at 225-1N-07 3M Center, St. Paul, Minnesota, its successors, and assigns, the entire right, title, and interest in and to the said invention and application, and in and to any division or continuation (in whole or in part) of said application, and in and to any and all improvements in the said invention made by us or any of us or made jointly with others (provided any such improvement is made during, or within one year after the termination of, the employment by the said Company of whichever of us, solely or jointly with one or more others, has made the same), and in and to any and all Letters Patent, reexaminations, reissues, or extensions thereof, of the United States of America and countries foreign thereto (including the right to apply for Letters Patent, Utility Models, or Inventors' Certificates in foreign countries in its own name and to claim any priority rights for such foreign applications to which such applications are entitled under international conventions, treaties, or otherwise), which have been or may be granted thereon or on any divisional, continuation (in whole or in part), renewal, reexamination, reissue, or other or further application based in whole or in part upon the said invention or improvements thereon, to be held and enjoyed as fully and exclusively as they would have been by us or any of us had this assignment and transfer not been made;

We do further agree for ourselves and for our heirs, executors, and administrators, to execute and deliver without further consideration any further applications, assignments, and documents, and to perform such other acts as we lawfully may, that may be deemed necessary by the said Company, its successors, assigns, and nominees, fully to secure its right, title and interest as aforesaid and to obtain or maintain Letters Patent, Utility Models or Inventors' Certificates in any and all countries;

And we do hereby authorize and request the Commissioner of Patents to issue any and all Letters Patent which may be granted upon any of the said applications, to the said Riker Laboratories, Inc., as the assignee of the entire right, title, and interest therein.

In witness whereof, we have hereunto signed our names on the day and year set forth below.

Steven M. Wick

Helen Jensen Schultz

Gregory R. Nelson

Amit K. Mitra

Stephen M. Berge

STATE OF MINNESOTA
} SS.
COUNTY OF RAMSEY

On this 29th day of November, 1989, before me personally appeared the above-named Steven M. Wick, Helen Jensen Schultz, Gregory R. Nelson, Amit K. Mitra and Stephen M. Berge personally known to me, and known by me to be the persons described in and who executed the foregoing instrument, and who acknowledged that they executed the same as their free act and deed, on the day and year aforesaid.

(Seal)

PATRICIA A. OLSEN
NOTARY PUBLIC—MINNESOTA
RAMSEY COUNTY
My Comm. Expires July 27, 1995

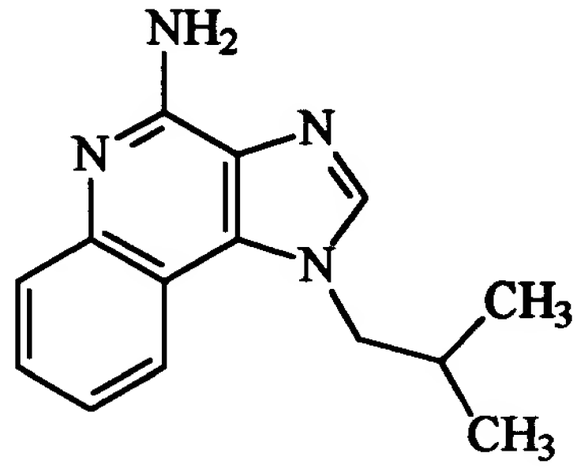
Notary Public

3M Office of Patent Counsel
P.O. Box 33427
St. Paul, Minnesota 55133-3427
U.S.A.

102689/8.12

STATEMENT OF AUTHORIZATION

Minnesota Mining & Manufacturing Co. (3M) has applied for marketing approval for the product ALDARA™ (imiquimod) 5% cream. The product contains the active ingredient imiquimod, or 1-(2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine. The compound has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3. Its structural formula is:



Having successfully completed the regulatory review for the above identified active ingredient under §505(b) of the Food, Drug and Cosmetic Act (21 U.S.C. §355(b)), 3M was granted approval by the Food and Drug Administration to market ALDARA™ (imiquimod) 5% cream on February 27, 1997.

3M hereby authorizes Riker Laboratories, Inc. (Riker), the owner of U.S. Patent Nos.4,689,338 and 5,238,944, to use 3M's regulatory review activities to obtain an extension of term on one of the aforementioned patents.

Date: April 3, 1997

Ted K. Ringsred
Registration No. 35,658

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PATENT

Docket No. 43682USA5C

DECLARATION UNDER 37 CFR 1.740(a)(17)

This Application is submitted pursuant to extension of the term of U.S. Patent No. 5,238,944, through its undersigned patent attorney authorized to practice before the Patent and Trademark Office and who has general authority from the owner to act on behalf of the owner in patent matters. The undersigned, as agent for Riker Laboratories, Inc., the owner of said patent, hereby declares:

THAT I am registered to practice before the Patent and Trademark Office and am making this declaration as a patent attorney who has general authority to act on behalf of the applicant in patent matters;

THAT I have reviewed and understand the contents of the attached application papers consisting of a 13 page Application and Exhibits A, B, C and D thereto;

THAT I believe U.S. Patent No. 5,238,944 is subject to extension pursuant to 36 U.S.C. 156 and 37 CFR § 1.710;

THAT I believe an extension of 187 days is fully justified under 35 U.S.C. 156;

THAT I believe U.S. Patent No. 5,238,944 meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. 156 and 37 CFR § 1.720; and

THAT all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 5,238,944.

DATE: April 22, 1997

Ted K. Ringsred
Registration No. 35,658

TKR\mlh
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 5,238,944

POWER OF ATTORNEY

Honorable Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D. C. 20231

Sir:

RIKER LABORATORIES, INC., the owner of U.S. Patent No. 5,238,944, by a written assignment recorded on November 15, 1985, and found at Reel 4485, Frame 139, hereby appoints Gary L. Griswold (Reg. No. 25,396), Walter N. Kirn (Reg. No. 21,196), Terryl K. Qualey (Reg. No. 25,148), Warren R. Bovee (Reg. No. 26,434), Gerald F. Chernivec (Reg. No. 26,537), Douglas B. Little (Reg. No. 28,439), David R. Cleveland (Reg. No. 29,524), and Ted K. Ringsred (Reg. No. 35,658) all registered to practice before the Patent and Trademark Office as its attorneys with full power of substitution and revocation to transact all business in the Patent and Trademark Office in connection with U.S. Patent No. 5,238,944, including, but not limited to, filing for patent term extension under 35 USC § 156. The assignee requests that all correspondence and telephone communications be directed to the following person at the mailing address and telephone number hereafter given:

Ted K. Ringsred
3M/Office of Intellectual Property Counsel
P.O. Box 33427
St. Paul, Minnesota 55133-3427
Telephone: (612) 736-5839

The assignee further gives general authority to Ted K. Ringsred to act on its behalf in patent matters. This includes the authority to make the declaration referred to in 37 CFR § 1.740(b).

The undersigned hereby declares that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and

further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent.

RIKER LABORATORIES, INC.

Dated: 4-17-97

By: Mark E. DuVal

Mark E. DuVal
Secretary

TKR\mlh
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EXHIBIT A

TEXT OF THE LABELLING FOR THE DRUG

Final Draft Package Insert

ALDARA™

[al dar' a]

(imiquimod)

Cream, 5%

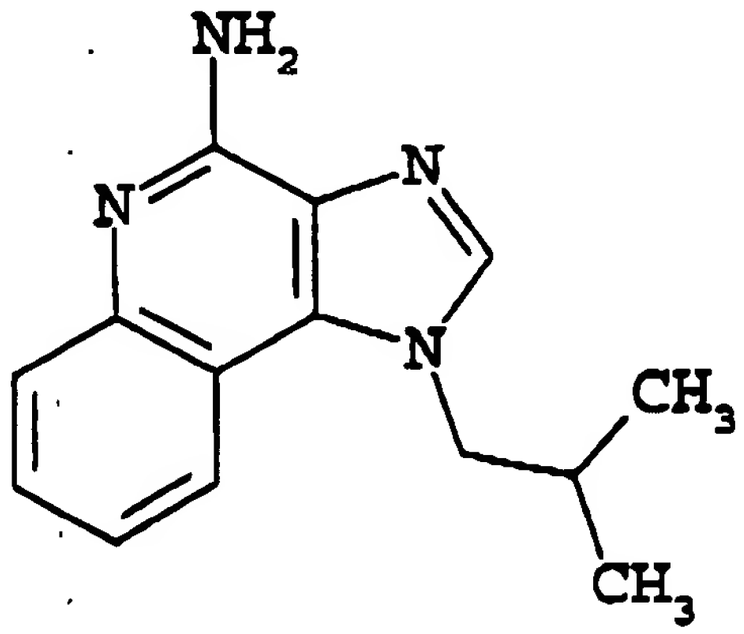
For Dermatologic Use Only -

Not for Ophthalmic Use.

DESCRIPTION

Aldara™ is the brand name for imiquimod which is an immune response modifier.[1] Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.[2]

Chemically, imiquimod is 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine.[3] Imiquimod has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3.[4] Its structural formula is:



CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of imiquimod in treating genital/perianal warts is unknown. Imiquimod has no direct antiviral activity in cell culture.[5] Mouse skin studies suggest that imiquimod induces cytokines including interferon-α. However, the clinical relevance of these findings is unknown.[6]

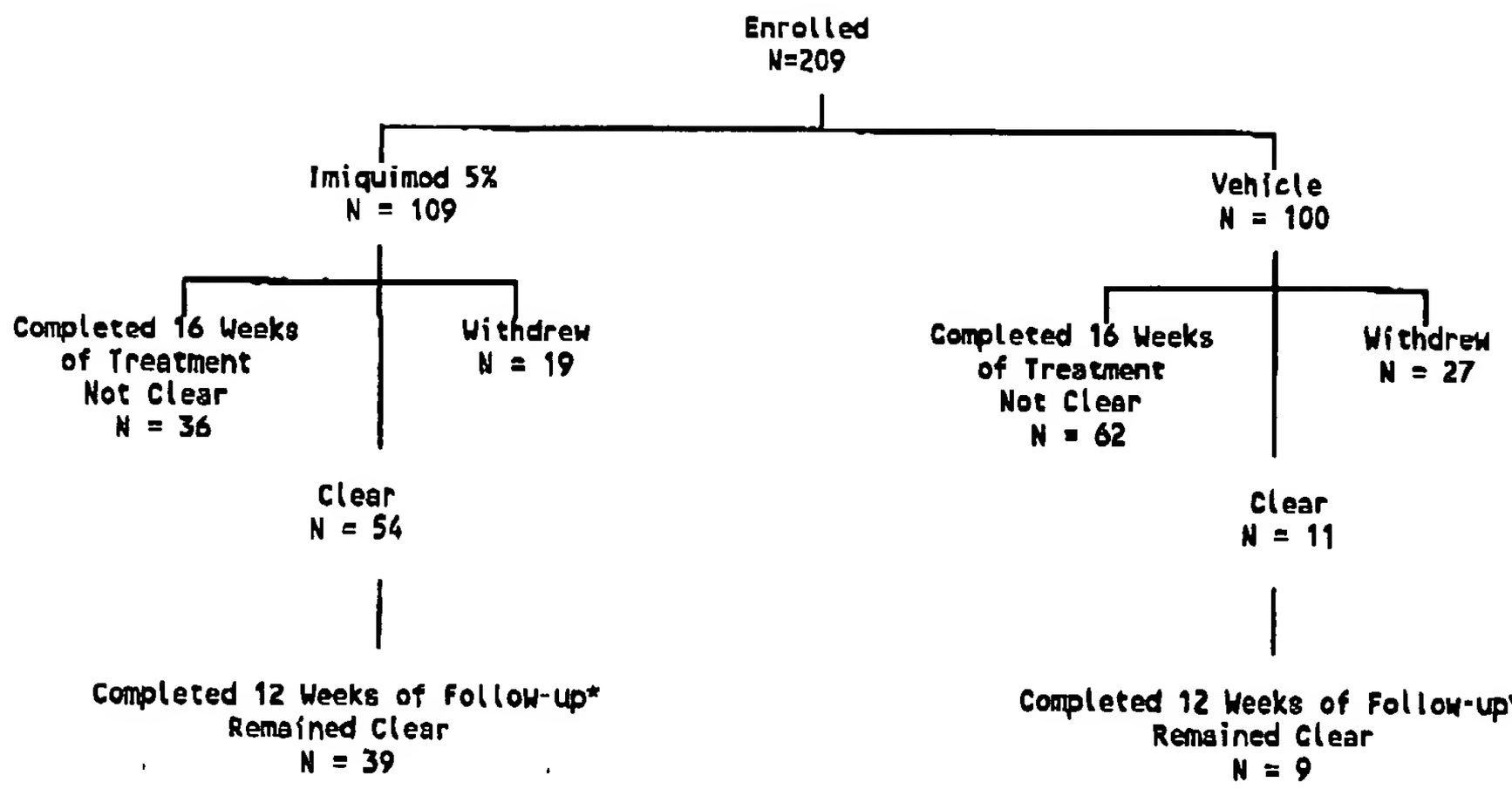
Pharmacokinetics

Percutaneous absorption of [^{14}C] imiquimod was minimal in a study involving 6 healthy subjects treated with a single topical application (5 mg) of [^{14}C] imiquimod cream formulation. No radioactivity was detected in the serum (lower limit of quantitation: 1 ng/mL) and < 0.9% of the radiolabelled dose was excreted in the urine and feces following topical application.[7]

CLINICAL STUDIES

In a double-blind, placebo-controlled clinical trial, 209 otherwise healthy patients 18 years of age and older with genital/perianal warts were treated with Aldara 5% cream or vehicle control 3X/week for a maximum of 16 weeks.[8] The median baseline wart area was 69 mm^2 (range 8 to 5525 mm^2).[9] Patient accountability is shown in the figure below.[10]

1004-IMIQ Patient Accountability



* The other patients were either lost to follow-up or experienced recurrences.

Data on complete clearance are listed in the table below. The median time to complete wart clearance was 10 weeks.[10]

CLEARANCE - STUDY 1004

	Treatment	Patients with Complete Clearance of Warts	Patients Without Follow-up	Patients with Warts Remaining at Week 16
Overall	imiquimod 5% (n=109)	50%	17%	33%
	vehicle (n=100)	11%	27%	62%
Females	imiquimod 5% (n=46)	72%	11%	17%
	vehicle (n=40)	20%	33%	48%
Males	imiquimod 5% (n=63)	33%	22%	44%
	vehicle (n=60)	5%	23%	72%

INDICATIONS AND USAGE

Aldara 5% cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in adults.[11]

CONTRAINDICATIONS

None known

WARNINGS

Aldara cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and is not recommended for these conditions.[12]

PRECAUTIONS

General

Local skin reactions such as erythema, erosion, excoriation/flaking, and edema are common.[13] Should severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with Aldara cream can be resumed after the skin reaction has subsided.[14] There is no clinical experience with Aldara cream therapy immediately following the treatment of genital/perianal warts with other cutaneously applied drugs; therefore, Aldara cream administration is not recommended until genital/perianal tissue is healed from any previous drug or surgical treatment.[15] Aldara has the potential to exacerbate inflammatory conditions of the skin.[16]

Information for Patients

Patients using Aldara 5% cream should receive the following information and instructions[17]: The effect of Aldara 5% cream on the transmission of genital/perianal warts is unknown. Aldara 5% cream may weaken condoms and vaginal diaphragms.[18] Therefore, concurrent use is not recommended.

1. This medication is to be used as directed by a physician. It is for external use only. Eye contact should be avoided.
2. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
3. Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin.
4. It is recommended that 6-10 hours following Aldara 5% cream application the treatment area be washed with mild soap and water.

5. It is common for patients to experience local skin reactions such as erythema, erosion, excoriation/flaking, and edema at the site of application or surrounding areas. Most skin reactions are mild to moderate.[19] Severe skin reactions can occur and should be reported promptly to the prescribing physician.
6. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.[20]
7. Patients should be aware that new warts may develop during therapy, as Aldara is not a cure.

Carcinogenicity, Mutagenesis, and Impairment of Fertility

Rodent carcinogenicity data are not available.[21] Imiquimod was without effect in a series of eight different mutagenicity assays including Ames, mouse lymphoma, CHO chromosome aberration, human lymphocyte chromosome aberration, SHE cell transformation, rat and hamster bone marrow cytogenetics, and mouse dominant lethal test.[22] Daily oral administration of imiquimod to rats, at doses up to 8 times the recommended human dose on a mg/m^2 basis throughout mating, gestation, parturition and lactation, demonstrated no impairment of reproduction.[23]

Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Imiquimod was not found to be teratogenic in rat or rabbit teratology studies. In rats at a high maternally toxic dose (28 times human dose on a mg/m^2 basis), reduced pup weights and delayed ossification were observed. In developmental studies with offspring of pregnant rats treated with imiquimod (8 times human dose), no adverse effects were demonstrated.[23]

Nursing Mothers

It is not known whether topically applied imiquimod is excreted in breast milk.

Pediatric Use

Safety and efficacy in patients below the age of 18 years have not been established.[15,24]

ADVERSE REACTIONS

In controlled clinical trials, the most frequently reported adverse reactions were those of local skin and application site reactions; some patients also reported systemic reactions. These reactions were usually mild to moderate in intensity; however, severe reactions were reported with 3X/week application. **These reactions were more frequent and more intense with daily application than with 3X/week application.**[25] Overall, in the 3X/week application clinical studies, 1.2% (4/327) of the patients discontinued due to local skin/application site reactions.[26] The incidence and severity of local skin reactions during controlled clinical trials are shown in the following table.[27]

3X/WEEK APPLICATION
WART SITE REACTION AS ASSESSED BY INVESTIGATOR

	MILD/MODERATE				SEVERE			
	FEMALES		MALES		FEMALES		MALES	
	5% Imiquimod N=114	Vehicle N=99	5% Imiquimod N=156	Vehicle N=157	5% Imiquimod N=114	Vehicle N=99	5% Imiquimod N=156	Vehicle N=157
Erythema	61%	21%	54%	22%	4%	0%	4%	0%
Erosion	30%	8%	29%	6%	1%	0%	1%	0%
Excoriation/ Flaking	18%	8%	25%	8%	0%	0%	1%	0%
Edema	17%	5%	12%	1%	1%	0%	0%	0%
Induration	5%	2%	7%	2%	0%	0%	0%	0%
Ulceration	5%	1%	4%	1%	3%	0%	0%	0%
Scabbing	4%	0%	13%	3%	0%	0%	0%	0%
Vesicles	3%	0%	2%	0%	0%	0%	0%	0%

Remote site skin reactions were also reported in female and male patients treated 3X/week with imiquimod 5% cream. The severe remote site skin reactions reported for females were erythema (3%), ulceration (2%), and edema (1%); and for males, erosion (2%), and erythema, edema, induration, and excoriation/flaking (each 1%).[28]

Adverse events judged to be probably or possibly related to Aldara reported by more than 5% of patients are listed below; also included are soreness, influenza-like symptoms and myalgia.[29]

	3X/WEEK APPLICATION			
	FEMALES		MALES	
	5% Imiquimod (n=117)	Vehicle (n=103)	5% Imiquimod (n=156)	Vehicle (n=158)
APPLICATION SITE DISORDERS:				
APPLICATION SITE REACTIONS				
Wart Site:				
Itching	32%	20%	22%	10%
Burning	26%	12%	9%	5%
Pain	8%	2%	2%	1%
Soreness	3%	0%	0%	1%
FUNGAL INFECTION [a]	11%	3%	2%	1%
SYSTEMIC REACTIONS:				
Headache	4%	3%	5%	2%
Influenza-like symptoms	3%	2%	1%	0%
Myalgia	1%	0%	1%	1%

[a]: Incidences reported without regard to causality with Aldara.[30]

Adverse events judged to be possibly or probably related to Aldara and reported by more than 1% of patients include: **Application Site Disorders: Wart Site Reactions** (burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness); **Remote Site Reactions** (bleeding, burning, itching, pain, tenderness, tinea cruris); **Body as a Whole:** fatigue, fever, influenza-like symptoms; **Central and Peripheral Nervous System Disorders:** headache; **Gastro-Intestinal System Disorders:** diarrhea; **Musculo-Skeletal System Disorders:** myalgia.[29]

OVERDOSAGE

Overdosage of Aldara 5% cream in humans is unlikely due to minimal percutaneous absorption.[7,31] Animal studies reveal a rabbit dermal lethal imiquimod dose of greater than 1600 mg/m^2.[32] Persistent topical overdosing of Aldara 5% cream could result in severe local skin reactions.[25] The most clinically serious adverse event reported following multiple oral imiquimod doses of >200 mg was hypotension which

resolved following oral or intravenous fluid administration.[33]

DOSAGE AND ADMINISTRATION

Aldara cream is to be applied 3 times per week, prior to normal sleeping hours, and left on the skin for 6-10 hours. Following the treatment period cream should be removed by washing the treated area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday application prior to sleeping hours. Aldara treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks.[34] Local skin reactions (erythema) at the treatment site are common.[13] A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. Treatment may resume once the reaction subsides.[14] Non-occlusive dressings such as cotton gauze or cotton underwear may be used in the management of skin reactions.[35] The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of Aldara therapy. Handwashing before and after cream application is recommended. Aldara 5% cream is packaged in single-use packets which contain sufficient cream to cover a wart area of up to 20 cm^2; use of excessive amounts of cream should be avoided. Patients should be instructed to apply Aldara cream to external genital/perianal warts. A <u>thin</u> layer is applied to the wart area and rubbed in until the cream is no longer visible. The application site is not to be occluded.[17]

HOW SUPPLIED

Aldara (imiquimod) cream, 5%, is supplied in single-use packets which contain 250 mg of the cream.[36] Available as: box of 12 packets NDC 0089-0610-12, and box of 30 packets NDC 0089-0610-30. Do not store above 30°C (86°F). Avoid freezing.[37]

Caution: Federal Law prohibits dispensing without prescription.

Imiquimod Cream 5%
Application Summary
Revised Section 2.1.4

2.1.4 References

[table 1 of 2]

Reference No.	Application Summary Location	Technical Summary Location
1	V 2.1 p 117	V 2.4 p 2
2	V 2.1 p 108	V 1.4 p 2
3	V 2.1 p 103	V 1.1 p 6
4	V 2.1 p 104	V 1.1 p 7
5	V 2.1 p 117	V 2.7 p 216-231
6	V 2.1 p 124-128,147-148	V 2.5 p 169-179
7	V 2.1 p 170-171,175-176	V 2.28 p 70-72, 74-76
8	V 2.1 p 212	V 2.44 p 29, 33, 57 V 2.159 p 92, 96, 120
9	---	V 2.44 p 65-66,147 V 2.159 p 128-129,210
10	V 2.1 p 212-213	V 2.44 p 68-69, 148, 207 V 2.159 p 131-132, 211, 270
11	V 2.1 p 190-191,206-207	V 2.44 p 28, 33 V 2.159 p 91, 96
12	V 2.1 p 190-191	V 2.44 p 37 V 2.159 p 100
13	V 2.1 p 258-259	V 2.146 p 26, 27 V 2.254 p 26, 27
14	---	V 2.146 p 108 V 2.254 p 108
15	---	V 2.45 p 335-338 V 2.160 p 335-338
16	V 2.1 p 122	V 2.4 p 2
17	---	V 2.45 p 354-356, 394-395 V 2.160 p 354-356, 394-395
18	NDA 20-723 Amendment dated February 7, 1997	
19	V 2.1 p 199,202,259	V 2.146 p 88 V 2.254 p 88
20	V 2.1 p 265-267	V 2.146 p 259 V 2.254 p 259

Imiquimod Cream 5%
Application Summary
Revised Section 2.1.4

2.1.4 References

[table 2 of 2]

Reference No.	Application Summary Location	Technical Summary Location
21	---	V 2.4 p 89-90, 112
22	V 2.1 p 158-159	V 2.4 p 234
23	V 2.1 p 157-158	V 2.4 p 201-203 V 2.23 p 350-353, 358-361
24	V 2.1 p 208	V 2.145 p 28-29 V 2.253 p 28-29 V 2.146 p 39 V 2.254 p 39
25	V 2.1 p 258-261	V 2.146 p 88,105,110,116,168,269 V 2.254 p 88,105,110,116,168,269
26	V 2.1 p 263	V 2.146 p 175-176 V 2.254 p 175-176
27	V 2.1 p 259	V 2.147 p 163,171 V 2.255 p 163,171
28	---	V 2.147 p 165,173 V 2.255 p 165,173
29	V 2.1 p 260-261	V 2.148 p 90-95, 119-121 V 2.256 p 90-95, 119-121
30	---	V 2.148 p 48,55 V 2.156 p 48,55
31	V 2.1 p 170-171,178	V 2.29 p 47, 51-52 V 2.28 p 12-13 V 2.30 p 44-45, 55
32	V 2.1 p 137	V 2.4 p 65
33	---	V 2.152 p 307-308 V 2.260 p 307-308
34	V 2.1 p 199,206	V 2.45 p 333 V 2.160 p 333
35	---	V 2.45 p 359 V 2.160 p 359
36	V 2.1 p 110	V 1.4 p 105
37	V 2.1 p 112	V 1.4 p 103

EXHIBIT B

US005238944A

United States Patent [19]

Wick et al.

[11] Patent Number: 5,238,944

[45] Date of Patent: Aug. 24, 1993

[54] **TOPICAL FORMULATIONS AND TRANSDERMAL DELIVERY SYSTEMS CONTAINING 1-ISOBUTYL-1H-IMIDAZO[4,5-C]QUINOLIN-4-AMINE**

[75] Inventors: **Steven M. Wick**, Mahtomedi; **Helen J. Schultz**, Falcon Heights, both of Minn.; **Gregory R. Nelson**, Hudson, Wis.; **Amit K. Mitra**, Woodbury; **Stephen M. Berge**, Shoreview, both of Minn.

[73] Assignee: **Riker Laboratories, Inc.**, St. Paul, Minn.

[21] Appl. No.: **845,323**

[22] Filed: **Mar. 3, 1992**

Related U.S. Application Data

[63] Continuation of Ser. No. 444,555, Nov. 30, 1989, abandoned, which is a continuation-in-part of Ser. No. 284,933, Dec. 15, 1988, abandoned.

[51] **Int. Cl.**[5] **A61K 31/44**; A61K 31/20

[52] **U.S. Cl.** **514/293**; 514/558; 514/947

[58] **Field of Search** 514/293, 784, 946, 947, 514/558

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,411,893	10/1983	Johnson et al.	514/293
4,689,338	8/1987	Gerster	514/293
4,695,465	9/1987	Kigasawa et al.	514/947
4,722,941	2/1988	Eckert et al.	514/784
4,746,515	5/1988	Cheng et al.	424/448
4,751,087	6/1988	Wick	514/784
4,863,970	9/1989	Patel et al.	514/947
4,908,389	3/1990	Mahjour et al.	514/947

FOREIGN PATENT DOCUMENTS

8809676 12/1988 PCT Int'l Appl. .

OTHER PUBLICATIONS

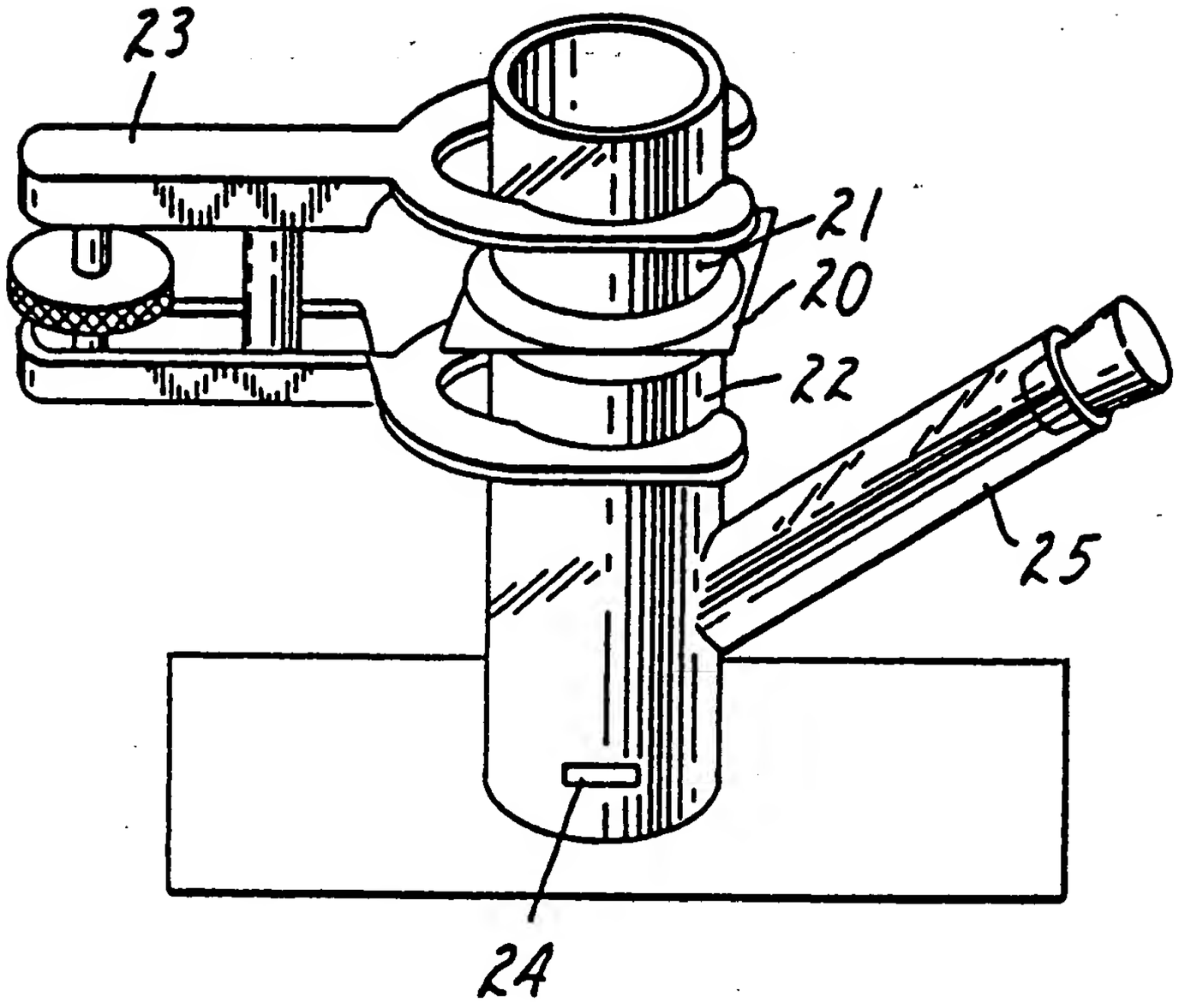
J. Pharm. Sci., 1984 (73) 1153 E. R. Cooper.
Yu et al. Pharm. Research (5), 457, 1988.
Loftsson et al. Pharm. Research (4) 346, 1987.
Chien et al. Pharm Research (5) 103, 1988.
Drug Dev. and Ind. Pharmacy, 1987 (13), 2363 Bharguva.
The Theory and Practice of Industrial Pharmacy Lachman, 2nd edition (1976) pp. 220–229.

Primary Examiner—Frederick E. Waddell
Assistant Examiner—Raymond J. Henley, III
Attorney, Agent, or Firm—Gary L. Griswold; Walter N. Kirn; Douglas E. Reedich

[57] **ABSTRACT**

Pharmaceutical formulations and adhesive-coated sheet materials for the topical and/or transdermal delivery of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine, including creams, ointments and pressure-sensitive adhesive compositions. Pharmacological methods of using the formulations and the adhesive-coated sheet materials of the invention in the treatment of viral infections.

13 Claims, 1 Drawing Sheet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TOPICAL FORMULATIONS AND TRANSDERMAL DELIVERY SYSTEMS CONTAINING 1-ISOBUTYL-1H-IMIDAZO[4,5-C]QUINOLIN-4-AMINE

This is a continuation of application Ser. No. 07/444,555 filed Nov. 30, 1989, now abandoned, which is a continuation-in-part of U.S. Ser. No. 07/284,933 filed Dec. 15, 1988 now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention pertains to pharmaceutical formulations for the topical or transdermal delivery of drugs. More particularly, it pertains to creams, ointments, pressure sensitive adhesive coatings, and adhesive-coated sheet materials that contain compounds that enhance skin penetration of drugs.

2. Description of the Related Art

The compound 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine is disclosed in U.S. Pat. No. 4,689,338 and described therein as an antiviral agent and as an interferon inducer. A variety of formulations for topical administration of this compound are also described.

U.S. Pat. No. 4,751,087 discloses the use of a combination of ethyl oleate and glyceryl monolaurate as a skin penetration enhancer for nitroglycerine, with all three components being contained in the adhesive layer of a transdermal patch.

U.S. Pat. No. 4,411,893 discloses the use of N,N-dimethyldodecylamine-N-oxide as a skin penetration enhancer in aqueous systems.

U.S. Pat. No. 4,722,941 discloses readily absorbable pharmaceutical compositions that comprise a pharmacologically active agent distributed in a vehicle comprising an absorption-enhancing amount of at least one fatty acid containing 6 to 12 carbon atoms and optionally a fatty acid monoglyceride. Such compositions are said to be particularly useful for increasing the absorption of pharmacologically active bases.

U.S. Pat. No. 4,746,515 discloses a method of using glyceryl monolaurate to enhance the transdermal flux of a transdermally deliverable drug through intact skin.

SUMMARY OF THE INVENTION

The present invention provides a substantially non-irritating pharmaceutical formulation for topical and/or transdermal administration of the agent 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which formulation comprises:

a) 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine in an amount of about 0.5 percent to about 9 percent by weight based on the total weight of the formulation; and

b) a pharmaceutically acceptable vehicle for the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which vehicle comprises a fatty acid selected from the group consisting of isostearic acid, oleic acid and a combination thereof in a total amount of about 3 percent to about 45 percent by weight based on the total weight of the formulation. The formulation is further characterized in that when tested in the hairless mouse skin model described herein, the formulation provides a penetration of the agent of at least about 10% (and preferably at least about 15%) of the total amount of the agent contained in the formulation in 24 hours.

The salient elements of a pharmaceutical formulation according to the invention are (a) 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and (b) a fatty acid, i.e., isostearic and/or oleic acid. A pharmaceutical formulation of the invention can be in any form known to the art, such as a cream, an ointment, or a pressure-sensitive adhesive composition, each form containing the necessary elements in particular amounts and further containing various additional elements.

A cream of the invention preferably contains about 1 percent to about 5 percent by weight of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, based on the total weight of the cream; about 5 percent to about 25 percent by weight of fatty acid, based on the total weight of the cream; and optional ingredients such as emollients, emulsifiers, thickeners, and/or preservatives.

An ointment of the invention contains an ointment base in addition to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and fatty acid. An ointment of the invention preferably contains about 0.5 percent to about 9 percent, and more preferably about 0.5 percent to about 5 percent by weight 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine; about 3 percent to about 45 percent, more preferably about 3 percent to about 25 percent by weight fatty acid; and about 60 percent to about 95 percent by weight ointment base, all weights being based on the total weight of the ointment. Optionally, an ointment of the invention can also contain emulsifiers, emollients and thickeners.

A pressure-sensitive adhesive composition of the invention contains 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine, fatty acid, and an adhesive. The adhesives utilized in a pressure sensitive adhesive composition of the invention are preferably substantially chemically inert to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine. A pressure sensitive adhesive composition of the invention preferably contains about 0.5 percent to about 9 percent by weight, more preferably of about 3 percent to about 7 percent by weight 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine; about 10 percent to about 40 percent by weight, more preferably of about 15 percent to about 30 percent by weight, and most preferably about 20 percent to about 30 percent by weight of fatty acid; all weights being based on the total weight of the pressure sensitive adhesive composition.

Optionally, pressure sensitive adhesive compositions of the invention can also contain one or more skin penetration enhancers. The total amount of skin penetration enhancer(s) present in a pressure sensitive adhesive composition of the invention is preferably about 3 percent to about 25 percent by weight, and more preferably about 3 percent to about 10 percent by weight based on the total weight of the pressure sensitive adhesive composition.

A pressure sensitive adhesive coated sheet material of the invention can be made from a pressure-sensitive adhesive composition of the invention in the form of an article such as a tape, a patch, a sheet, or a dressing.

A formulation of the invention can be used to topically and/or transdermally administer 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine for treating viral infections, for example Type I or Type II Herpes simplex infections.

BRIEF DESCRIPTION OF THE DRAWING

The invention will be described below with reference to the accompanying Drawing, which is an isometric view of a diffusion cell for measuring penetrability of

1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine across mammalian skin.

DETAILED DESCRIPTION OF THE INVENTION

As used in the specification and claims, the phrase "substantially non-irritating" designates formulations that do not cause unacceptable skin irritation in conventional repeat skin irritation tests in albino rabbits such as that described in Draize et al., "Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics", prepared by the Division of Pharmacology of the Food and Drug Administration, published originally in 1959 by the Association of Food and Drug Officials of the United States, Topeka, Kans. (2nd printing 1965), incorporated herein by reference.

The present invention provides pharmaceutical formulations such as creams, ointments and adhesive coatings that contain 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine and a fatty acid such as isostearic and/or oleic acid. The formulations of the invention provide desirable skin penetrability of the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine.

The compound 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine is a known antiviral agent that is also known to induce interferon biosynthesis. It can be prepared using the method disclosed in U.S. Pat. No. 4,689,338, the disclosure of which is incorporated herein by reference. The compound can be used to treat viral infections such as Type I or Type II Herpes simplex infections and genital warts. Furthermore, the fact that the compound is an interferon inducer suggests that it, and therefore formulations containing it, might be useful in the treatment of numerous other diseases, such as rheumatoid arthritis, warts, eczema, hepatitis B, psoriasis, multiple sclerosis, essential thrombocythaemia, and cancer, such as basal cell carcinoma and other neoplastic diseases. The amount of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine present in a formulation of the invention will be an amount effective to treat the targeted disease state to prevent the recurrence of such a disease or to promote immunity against such a disease. The amount is preferably about 0.5 percent to about 9 percent by weight based on the total weight of a formulation.

A fatty acid such as isostearic acid, oleic acid or a mixture thereof is incorporated into a formulation of the invention. The total amount of fatty acid present in a formulation is preferably about 3 percent to about 45 percent by weight based on the total weight of a formulation.

A pharmaceutical formulation of the invention can be in a form such as a cream, an ointment, a pressure-sensitive adhesive composition, or other forms known to those skilled in the art, each particular form containing 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and fatty acid in particular amounts, and optionally containing various additional elements. The preferred amounts of drug and fatty acid, and the amounts and types of optional elements used in formulations of the invention are discussed below with particular reference to creams, ointments, and adhesive compositions.

A cream according to the invention contains 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and fatty acid.

The amount of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine present in a cream is preferably about 0.5 percent to about 9 percent by weight, and more preferably about 1 percent to about 5 percent by weight, based on the total weight of the cream.

The total amount of fatty acid present in a cream of the invention is preferably about 3 percent to about 45 percent by weight, and more preferably about 5 percent to about 25 percent by weight, based on the total weight of the cream.

Optionally, a cream of the invention can contain emollients, emulsifiers, thickeners, and/or preservatives.

Emollients such as long chain alcohols, e.g., cetyl alcohol, stearyl alcohol and cetearyl alcohol; hydrocarbons such as petrolatum and light mineral oil; or acetylated lanolin can be included in a cream of the invention. A cream can contain one or more of these emollients. The total amount of emollient in a cream of the invention is preferably about 5 percent to about 30 percent, and more preferably about 5 percent to about 10 percent by weight based on the total weight of the cream.

Emulsifiers such as nonionic surface active agents, e.g., polysorbate 60 (available from ICI Americas), sorbitan monostearate, polyglyceryl-4 oleate, and polyoxyethylene(4)lauryl ether or trivalent cationic a cream of the invention. A cream can contain one or more emulsifiers. Generally the total amount of emulsifier is preferably about 2 percent to about 14 percent, and more preferably about 2 percent to about 6 percent by weight based on the total weight of the cream.

Pharmaceutically acceptable thickeners, such as Veegum TM K (available from R. T. Vanderbilt Company, Inc.), and long chain alcohols (i.e. cetyl alcohol, stearyl alcohol or cetearyl alcohol) can be used. A cream can contain one or more thickeners. The total amount of thickener present is preferably about 3 percent to about 12 percent by weight based on the total weight of the cream.

Preservatives such as methylparaben, propylparaben and benzyl alcohol can be present in a cream of the invention. The appropriate amount of such preservative(s) is known to those skilled in the art.

Optionally, an additional solubilizing agent such as benzyl alcohol, lactic acid, acetic acid, stearic acid or hydrochloric acid can be included in a cream of the invention. If an additional solubilizing agent is used, the amount present is preferably about 1 percent to about 12 percent by weight based on the total weight of the cream.

Optionally, a cream of the invention can contain a humectant such as glycerin, skin penetration enhancers such as butyl stearate, and additional solubilizing agents.

It is known to those skilled in the art that a single ingredient can perform more than one function in a cream, i.e., cetyl alcohol can serve both as an emollient and as a thickener.

Generally, a cream consists of an oil phase and a water phase mixed together to form an emulsion. Preferably, the amount of water present in a cream of the invention is about 45 percent to about 85 percent by weight based on the total weight of the cream.

The oil phase of a cream of the invention can be prepared by first combining the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and the fatty acid (if the cream contains benzyl alcohol it can also be added at this point) and heating with occasional stirring to a temperature of about 50° C. to 85° C. When the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine appears to be

completely dissolved, the remaining oil phase ingredients are added and heating is continued until dissolution appears to be complete.

The water phase can be prepared by combining all other ingredients and heating with stirring until dissolution appears to be complete.

The creams of the invention are generally prepared by adding the water phase to the oil phase with both phases at a temperature of about 65° C. to 75° C. The resulting emulsion is mixed with a suitable mixer apparatus to give the desired cream.

An ointment of the invention contains an ointment base in addition to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and fatty acid.

The amount of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine present in an ointment of the invention is preferably about 0.5 percent to about 9 percent, and more preferably about 0.5 percent to about 5 percent by weight based on the total weight of the ointment.

The total amount of fatty acid present in an ointment of the invention is preferably about 3 percent to about 45 percent, and more preferably about 3 percent to about 25 percent based on the total weight of the ointment.

A pharmaceutically acceptable ointment base such as petrolatum or polyethylene glycol 400 (available from Union Carbide) in combination with polyethylene glycol 3350 (available from Union Carbide) can be used. The amount of ointment base present in an ointment of the invention is preferably about 60 percent to about 95 percent by weight based on the total weight of ointment.

Optionally, an ointment of the invention can also contain emollients, emulsifiers and thickeners. The emollients, emulsifiers, and thickeners and the preferred amounts thereof described above in connection with creams are also generally suitable for use in an ointment of the invention.

An ointment according to the invention can be prepared by combining 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine with fatty acid and heating with occasional stirring to a temperature of about 65° C. When the 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine appears to be completely dissolved, the remaining ingredients are added and heated to about 65° C. The resulting mixture is mixed with a suitable mixer while being allowed to cool to room temperature.

A pressure-sensitive adhesive composition of the invention contains 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine, fatty acid, and a pressure sensitive adhesive polymer.

The amount of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine present in a pressure sensitive adhesive composition of the invention is preferably about 0.5 percent to about 9 percent by weight, and more preferably about 3 percent to about 7 percent by weight based on the total weight of the adhesive composition. The amount of fatty acid present is preferably about 10 percent to about 40 percent by weight, more preferably about 15 percent to about 30 percent by weight, and most preferably about 20 percent to about 30 percent by weight, based on the total weight of the adhesive composition.

Preferably, the adhesive polymer utilized in a pressure sensitive adhesive composition of the invention is substantially chemically inert to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine. The adhesive polymer is preferably present in an amount of about 55 percent to about 85 percent by weight based on the total weight of the composition. Suitable adhesive polymers include acrylic adhesives that contain, as a major constituent (i.e., at least about 80 percent by weight of all monomers in the polymer), a hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol, the alkyl alcohol containing 4 to 10 carbon atoms. Examples of suitable monomers are those discussed below in connection with the "A Monomer". These adhesive polymers can further contain minor amounts of other monomers such as the "B Monomers" listed below.

Preferred adhesives include acrylic pressure-sensitive adhesive copolymers containing A and B Monomers as follows: Monomer A is a hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol, the alkyl alcohol containing 4 to 10 carbon atoms, preferably 6 to 10 carbon atoms, more preferably 6 to 8 carbon atoms, and most preferably 8 carbon atoms. Examples of suitable A Monomers are n-butyl, n-pentyl, n-hexyl, isoheptyl, n-nonyl, n-decyl, isohexyl, 2-ethyloctyl, isooctyl and 2-ethylhexyl acrylates. The most preferred A Monomer is isooctyl acrylate.

Monomer B is a reinforcing monomer selected from the group consisting of acrylic acid; methacrylic acid; alkyl acrylates and methacrylates containing 1 to to 3 carbon atoms in the alkyl group; acrylamide; methacrylamide; lower alkyl-substituted acrylamides (i.e., the alkyl group containing 1 to 4 carbon atoms) such as tertiary-butyl acrylamide; diacetone acrylamide; n-vinyl-2-pyrrolidone; vinyl ethers such as vinyl tertiary-butyl ether; substituted ethylenes such as derivatives of maleic anhydride, dimethyl itaconate and monoethyl formate and vinyl perfluoro-n-butyrate. The preferred B Monomers are acrylic acid, methacrylic acid, the above-described alkyl acrylates and methacrylates, acrylamide, methacrylamide, and the above-described lower alkyl substituted acrylamides. The most preferred B Monomer is acrylamide.

In one embodiment of a pressure-sensitive adhesive composition of the invention, the pressure-sensitive adhesive copolymer containing A and B Monomers as set forth above preferably contains the A Monomer in an amount by weight of about 80 percent to about 98 percent of the total weight of all monomers in the copolymer. The A Monomer is more preferably present in an amount by weight of about 88 percent to about 98 percent, and is most preferably present in an amount by weight of about 91 percent to about 98 percent. The B Monomer in such a copolymer is preferably present in the pressure-sensitive adhesive copolymer in an amount by weight of about 2 percent to about 20 percent, more preferably about 2 percent to about 12 percent, and most preferably 2 to 9 percent of the total weight of the monomers in the copolymer.

In another embodiment of a pressure-sensitive adhesive composition of the invention, the adhesive copolymer comprises about 60 to about 80 percent by weight (and preferably about 70 to about 80 percent by weight) of the above-mentioned hydrophobic monomeric acrylic or methacrylic acid ester of an alkyl alcohol (i.e., Monomer A described above) based on the total weight of all monomers in the copolymer; about 4 to about 9 percent by weight based on the total weight of all monomers in the copolymer of a reinforcing monomer selected from the group consisting of acrylic acid, methacrylic acid, an alkyl acrylate or methacrylate containing 1 to 3 carbon atoms in the alkyl group, acrylamide, methacrylamide, a lower alkyl-substituted acryl-

amide, diacetone acrylamide and N-vinyl-2-pyrrolidone; and about 15 to about 35 percent by weight (and preferably about 15 to about 25 percent by weight) of vinyl acetate based on the total weight of all monomers in the copolymer. In this embodiment the preferred acrylic or methacrylic acid ester is isooctyl acrylate and the preferred reinforcing monomer is acrylamide.

The above described adhesive copolymers are known, and methods of preparation therefor are well known to those skilled in the art, having been described for example, in U.S. Pat. No. 24,906 (Ulrich), the disclosure of which is incorporated herein by reference. The polymerization reaction can be carried out using a free radical initiator such as an organic peroxide (e.g., benzoylperoxide) or an organic azo compound (e.g., 2,2'-azobis(2,4-dimethylpentanenitrile), available under the trade designation "Vazo 52" from DuPont).

Since pressure-sensitive adhesives such as those described above are inherently rubbery and tacky and are suitably heat and light stable, there is no need to add tackifiers or stabilizers. However, such can be added if desired.

Optionally, a pressure sensitive adhesive composition of the invention can also contain one or more skin penetration enhancers such as glyceryl monolaurate, ethyl oleate, isopropyl myristate, diisopropyl adipate and N,N-dimethyldodecylamine-N-oxide, either as a single ingredient or as a combination of two or more ingredients. The skin penetration enhancer(s) preferably form a substantially homogeneous mixture with the pressure sensitive adhesive polymer or copolymer. The total amount of skin penetration enhancer(s) present in a pressure sensitive adhesive composition of the invention is preferably about 3 percent to about 25 percent by weight, more preferably about 3 percent to about 10 percent by weight based on the total weight of the adhesive composition.

When the skin penetration enhancer is a single ingredient, it is preferably a skin penetration enhancer such as isopropyl myristate, diisopropyl adipate, ethyl oleate, or glyceryl monolaurate.

When a combination skin penetration enhancer is used, it is preferably a combination such as: ethyl oleate with glyceryl monolaurate; ethyl oleate with N,N-dimethyldodecylamine-N-oxide; glyceryl monolaurate with N,N-dimethyldodecylamine-N-oxide; and ethyl oleate with both glyceryl monolaurate and N,N-dimethyldodecylamine-N-oxide.

A pressure-sensitive adhesive composition of the invention can be prepared by combining dry adhesive, 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, fatty acid, and skin penetration enhancer(s) with an organic solvent. The preferred organic solvents are methanol and ethyl acetate. The total solids content of the adhesive coating is preferably in the range of about 15 percent to about 40 percent, and more preferably in the range of about 20 to about 35 percent based on the total weight of the adhesive coating. The resulting mixture is shaken or mixed for a period of about 20 to 72 hours. When this method is used it is preferred that the 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine be in micronized form (i.e., particle size of 1–2 microns in diameter). Optionally, the mixture can be heated during shaking.

In a preferred method, the 1-isobutyl-1H-imidazo-4,5-c]quinolin-4-amine is combined with the fatty acid and shaken at 40° C. until there appears to be complete dissolution. The remaining ingredients are added and the mixture is shaken for a period of about 20 to 72 hours.

The pressure-sensitive adhesive compositions described above are preferably coated onto one surface of a suitable backing of sheet material, such as a film, to form a pressure-sensitive adhesive coated sheet material. A pressure-sensitive adhesive coated sheet material of the invention can be prepared by knife coating a suitable release liner to a predetermined uniform thickness with a wet adhesive formulation. This adhesive coated release liner is then dried and laminated onto a backing using conventional methods. Suitable release liners include conventional release liners comprising a known sheet material, such as a polyester web, a polyethylene web, or a polystyrene web, or polyethylene-coated paper, coated with a suitable silicone-type coating such as that available under the trade designation Daubert 164Z, from Daubert Co. The backing can be occlusive, non-occlusive or a breathable film as desired. The backing can be any of the conventional materials for pressure-sensitive adhesive tapes, such as polyethylene, particularly low density polyethylene, linear low density polyethylene, high density polyethylene, randomly-oriented nylon fibers, polypropylene, ethylene-vinylacetate copolymer, polyurethane, rayon and the like. Backings that are layered, such as polyethylene-aluminum-polyethylene composites are also suitable. The backing should be substantially non-reactive with the ingredients of the adhesive coating. The presently preferred backing is low density polyethylene.

The pressure-sensitive adhesive coated sheet material of the invention can be made in the form of an article such as a tape, a patch, a sheet, a dressing or any other form known to those skilled in the art.

Preferably, an article in the form of a patch is made from an adhesive coated sheet material of the invention and applied to the skin of a mammal. The patch is replaced as necessary with a fresh patch to maintain the particular desired therapeutic effect of the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine.

The following test methods have been employed in the examples which thereafter follow.

In Vitro Test Method

Although animal skins are known to give significant quantitative differences in drug penetrability as compared to human skin, a rank order correlation is generally observed with various drugs (M. J. Bartek and J. A. LaBudde in "Animal Modes in Dermatology", H. Maibach, Ed., Churchill Livingstone, New York, 1975, pp. 103–119). Hairless mouse skin has been recommended as a readily available animal skin for use in diffusion cells with steroids and other small molecules (R. B. Stoughton, Arch. Derm., 99, 753 (1969), J. L. Cohen and R. B. Stoughton, J. Invest. Derm. 62, 507 (1974), R. B. Stoughton in "Animal Modes in Dermatology", pp. 121–131). In the specific test procedure used herein, hairless mouse skin removed from female hairless mice that were 40–80 days old (available from Jackson Laboratory, Strain HRS/J) was used. The skin was maintained on ice until use, and it was preferably used within 8 hours of sacrifice. The mouse skin was mounted on a diffusion cell of the type shown in the Drawing. The cell is modeled after those described in the literature, e.g., J. L. Cohen, R. B. Stoughton, *J. Invest. Derm.*, 62, 507 (1974) and R. B. Stoughton, *Arch. Derm.*, 99, 753 (1964). As shown in the Drawing, the mouse skin **20** was mounted epidermal side up between upper and

lower portions of the cell 21 and 22, which are held together by means of a ball joint clamp 23.

The portion of the cell below the mounted skin was completely filled with 0.1 N hydrochloric acid such that the receptor fluid contacted the skin. The receptor fluid was stirred using a magnetic stir bar 24 and a magnetic stirrer (not illustrated). The sampling port 25 was covered with a material such as Parafilm ® except when in use.

When a cream or ointment was evaluated, approximately 100 mg of the formulation was applied to the epidermal (upper) side of the skin to cover in an even layer only the area of the skin that would be in contact with the receptor fluid when the skin is mounted in the diffusion cell. When an adhesive coated sheet material was evaluated, the skin was mounted on the diffusion cell and a 2.056 cm^2 patch was applied to the skin and pressed to cause uniform contact to the skin. Generally, the cream or the patch was applied to the skin prior to the time the receptor fluid was added to the cell below the skin.

The cell was then placed in a constant temperature (32°±2° C.) chamber. To maintain constant temperature, the chamber utilized a heat exchanger coupled to a constant temperature bath, with a fan to circulate air. The receptor fluid was stirred by means of a magnetic stirring bar throughout the experiment to assure a uniform sample and a reduced diffusion barrier layer on the dermal side of the skin. A sample of receptor fluid was removed at specified times. The withdrawn receptor fluid was analyzed for drug content by conventional high pressure liquid chromatography as follows:

A 15 centimeter column containing Zorbax TM C_8 (an octylsilane, available from E. I. DuPont de Nemours & Company), 5 micron particle size, was used. The mobile phase was 35 percent acetonitrile/65 percent water (volume/volume) containing 0.2 percent tetramethylammonium hydroxide and 0.2 percent 1-dodecanesulfonate sodium, with the pH of the mobile phase adjusted to 2.0 with phosphoric acid. The flow rate was 2 ml per minute. Ultraviolet detection at 254 nanometers was used. The amount of drug penetrating the skin over the specified time period was calculated as a percentage of the dose applied to the skin.

This in vitro method is referred to as the hairless mouse skin model in the claims. For purposes of the claims where this model is referred to the values stated for skin penetration are the average of 4 independent determinations using a different mouse skin for each determination.

In Vivo Test Method

Formulations of the invention can also be evaluated in vivo for their ability to inhibit lesion formation in guinea pigs infected with Herpes simplex virus Type II and for their ability to induce interferon production in guinea pigs.

In the specific test method used herein, care was taken to be sure the formulation had optimal penetration by washing the backs of the guinea pigs with mild detergent before the formulations were applied. One treatment was given at 24 hours preinfection. When a cream or ointment was evaluated, 200 microliters of the formulation was applied topically to the back of the guinea pig. rubbed in, covered with a Hill-top Chamber and then wrapped with Medipore TM brand tape (commercially available from 3M). When an adhesive coated sheet material was evaluated, an article in the form of a patch of a specified size was applied to the back of the guinea pig and wrapped with Medipore TM brand tape. After the patch had been in place for 24 hours, it was removed and the guinea pig was infected with the virus as described below.

Female Hartley guinea pigs (150–200 grams) were abraded in the vaginal area with a dry cotton swab. The guinea pigs were then infected intravaginally with a cotton swab saturated with HSV-2 (1×10^{-5} plaque forming units/ml). The formulations of the invention were evaluated by comparing lesion development in treated and untreated animals. External lesions were scored daily for ten days, unless otherwise specified, using the following scale: 0, no lesion; 1, redness and swelling; 2, a few small vesicles; 3, several large vesicles; 4, large ulcers and necrosis; 5, paralysis. The percent Lesion Inhibition was calculated as follows 100−[(Sum of maximum lesion scores of treated group divided by the Sum of the maximum scores of infected control)×100].

Interferon levels in the guinea pigs was monitored by bleeding via cardiac puncture of anesthetized guinea pigs 17 to 24 hours after dosing. The serum of each animal was separately assayed for interferon activity as follows:

The serum was diluted and incubated with guinea pig fibroblast cells at 37° C. overnight in 96 well microtiter plates. The incubated cells were then challenged with an inoculum of mengovirus that is sufficient to kill untreated cells in two days. Two days after such a challenge, the cells were examined both microscopically and after staining with crystal violet to determine whether the cells remain intact The results were reported as activity/ml. Activity/ml indicates the highest dilution of serum that protects cells from virus challenge. An untreated guinea pig control typically exhibits an activity/ml of less than about 100, although activity/ml has been observed to exceed 100.

Inherent Viscosity Measurement

The inherent viscosity values reported in the Examples below were obtained by the conventional method used by those skilled in the art. The measurement of the viscosity of dilute solutions of the adhesive, when compared to controls run under the same conditions, clearly demonstrates the relative molecular weights. It is the comparative values that are significant; absolute figures are not required. In the examples, the inherent viscosity values were obtained using a Cannon-Fenske #50 viscometer to measure the flow time of 10 ml of a polymer solution (0.2 g polymer/deciliter tetrahydrofuran, in a water bath controlled at 25° C.). The examples and the controls were run under identical conditions. The test procedure followed and the apparatus used are explained in detail in the *Textbook of Polymer Science,* F. W. Billmeyer, Wiley-Interscience, 2nd Edition, 1971 under: Polymer chains and their characterization, D. Solution Viscosity and Molecular Size, pp 84–85, the disclosure of which is incorporated by reference.

The following examples are provided to illustrate the invention, but are not intended to be limiting thereof. Parts and percentages are by weight unless otherwise specified.

PREPARATIVE METHOD 1

Laboratory Scale Preparation of Isooctylacrylate/Acrylamide Copolymer

To a 114 gram narrow-mouth glass bottle were added: 18.6 g isooctyl acrylate, 1.4 g acrylamide, 0.04 g benzoyl peroxide, 27.0 g ethyl acetate and 3.0 g methanol. The solution was purged for thirty five seconds with nitrogen at a flow rate of one liter per minute. The bottle was sealed and placed in a rotating water bath at 55° C. for twenty-four hours to effect essentially complete polymerization. The polymer was diluted with ethyl acetate/methanol (90/10) to 23.2 percent solids and had a measured inherent viscosity of 1.26 dl/g in ethyl acetate.

PREPARATIVE METHOD 2

Pilot Plant Scale Preparation of Isooctylacrylate/Acrylamide Copolymer

155 kg isooctylacrylate, 11.6 kg acrylamide, 209.1 kg ethyl acetate and 23.2 kg methanol were charged to a clean, dry reactor. Medium agitation was applied. The batch was deoxygenated with nitrogen while heating to an induction temperature of 55° C. 114 g Lucidol TM 70 initiator (available from Pennwalt Corp.) mixed with 2.3 kg ethyl acetate was charged to the reactor. The temperature was maintained at 55° C. throughout the reaction. After 5.5 hours reaction time, 114 g Lucidol TM 70 mixed with 2.3 kg ethyl acetate were charged to the reactor. After 9.0 hours reaction time, an additional 114 g Lucidol TM 70 initiator mixed with 2.3 kg ethyl acetate were charged to the reactor. The reaction was continued until the percent conversion was greater than 98 percent as measured by gas chromatographic evaluation of residual monomer concentration. The resulting polymer solution was diluted to 25–28 percent solids with ethyl acetate/methanol (90/10) and had a measured Brookfield viscosity of 17,000–21,000 centipoises using spindle #4 at 12 rpm. The polymer had a measured inherent viscosity of 1.3–1.4 dl/g in ethyl acetate.

The above procedure was found to provide a pressure-sensitive adhesive that is equivalent in the practice of the present invention to a pressure-sensitive adhesive prepared according to PREPARATIVE METHOD 1.

A 25–30 percent solids solution of the isooctyl acrylate:acrylamide (93:7) adhesive copolymer in ethyl acetate/methanol (90:10) was coated onto a two-sided release liner using a knife-coater and coating at 0.5 mm in thickness. The adhesive-coated laminate was dried first at 82° C. for 3 minutes and then at 116° C. for 3 minutes. The dried adhesive coating was then stripped off the release liner and placed in a glass bottle. The foregoing procedure results in a reduction of the amount of any residual monomer in the adhesive copolymer.

PREPARATIVE METHOD 3

Preparation of Isooctyl Acrylate: Acrylamide: Vinyl Acetate (75:5:20) Copolymer

The procedure of PREPARATIVE METHOD 1 above acrylate, 8.0 g acrylamide, 32.0 g vinyl acetate, 0.32 g benzoyl peroxide, 216.0 g ethyl acetate and 24.0 g methyl alcohol. The resulting polymer was diluted with the ethyl acetate/methyl alcohol mixture to 21.52% solids. The adhesive polymer had a measured inherent viscosity of 1.40 dl/g in ethyl acetate at a concentration of 0.15 g/dl. Its Brookfield viscosity was 2,300 centipoise.

PREPARATIVE METHOD 4

Preparation of Isooctyl Acrylate Acrylamide: Vinyl Acetate (75:5:20) Copolymer

A master batch was prepared by combining 621.0 g of isooctyl acrylate, 41.4 g of acrylamide, 165.6 g of vinyl acetate, 1.656 g of 2,2'-azobis(2,4-dimethylpentanenitrile) (available from the DuPont Company as Vazo TM 52), 884.52 g of ethyl acetate and 87.48 g of methanol. A 400 g portion of the resulting solution was placed in an amber quart bottle. The bottle was purged for two minutes with nitrogen at a flow rate of one liter per minute. The bottle was sealed and placed in a rotating water bath at 45° C. for twenty-four hours to effect essentially complete polymerization. The copolymer was diluted with 250 g of ethyl acetate/methanol (90/10) to 26.05% solids and had a measured inherent viscosity of 1.27 dl/g in ethyl acetate at a concentration of 0.15 g/dl. Its Brookfield viscosity was 5580 centipoise.

EXAMPLE 1

A cream according to the present invention was prepared from the following ingredients:

	% by Weight	Amount
Oil Phase		
1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine	1.0	40.0 g
Isostearic acid	10.0	400.0 g
Benzyl alcohol	2.0	80.0 g
Cetyl alcohol	2.2	88.0 g
Stearyl alcohol	3.1	124.0 g
Polysorbate 60	2.55	102.0 g
Sorbitan monostearate	0.45	18.0 g
Aqueous Phase		
Glycerin	2.0	80.0 g
Methylparaben	0.2	8.0 g
Propylparaben	0.02	0.8 g
Purified water	76.48	3059.2 g

The materials listed above were combined according to the following procedure:

The glycerin, methylparaben, propylparaben and water were weighed into a 4 liter glass beaker then heated on a hot plate with stirring until the parabens isostearic acid and 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine were weighed into an 8 liter stainless steel beaker and heated on a hot plate until the amine was in solution (the temperature reached 69° C.). The benzyl alcohol, cetyl alcohol, stearyl alcohol, polysorbate 60 and sorbitan monostearate were added to the isostearic acid solution and heated on a hot plate until all material was dissolved (the temperature reached 75° C.). With both phases at approximately the same temperature (65°–75° C.), the water phase was added to the oil phase. The mixture was mixed with a homogenizer for 13 minutes then put into a cool water bath and mixed with a 3 inch propeller for 40 minutes (the temperature was 29° C.). The resulting cream was placed in glass jars.

EXAMPLES 2-9

Using the general method of Example 1, the cream formulations shown in Tables 1 and 2 were prepared.

TABLE 1

	% by Weight Example 2	3	4	5
Oil Phase				
1-Isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine	1.0	1.0	1.0	1.0
Isostearic acid	10.0	10.0	5.0	5.0
Benzyl alcohol	—	2.0	—	—
Cetyl alcohol	—	1.7	—	—
Stearyl alcohol	—	2.3	—	—
Cetearyl alcohol	6.0	—	6.0	6.0
Polysorbate 60	2.55	2.55	2.55	2.55
Sorbitan monostearate	0.45	0.45	0.45	0.45
Brij TM 30[a]	—	—	—	10.0
Aqueous Phase				
Glycerin	2.0	2.0	2.0	2.0
Methylparaben	0.2	0.2	0.2	0.2
Propylparaben	0.02	0.02	0.02	0.02
Purified water	77.78	77.78	82.78	72.78

Brij TM 30 (polyoxyethylene(4) lauryl ether) is available from ICI Americas, Inc.

TABLE 2

	% by Weight Example 6	7	8	9
Oil Phase				
1-Isobutyl-1H-imidazo-[4.5-c]quinolin-4-amine	1.0	1.0	1.0	1.0
Isostearic acid	10.0	25.0	10.0	6.0
Benzyl alcohol	—	2.0	—	2.0
Cetyl alcohol	—	2.2	1.7	—
Stearyl alcohol	—	3.1	2.3	—
Cetearyl alcohol	6.0	—	—	6.0
Polysorbate 60	2.55	3.4	2.55	2.55
Sorbitan monostearate	0.45	0.6	0.45	0.45
Brij TM 30	10.0	—	—	—
Aqueous Phase				
Glycerin	2.0	2.0	2.0	2.0
Methylparaben	0.2	0.2	0.2	0.2
Propylparaben	0.02	0.02	0.02	0.02
Purified water	67.78	60.48	79.78	79.78

EXAMPLE 10

A cream according to the present invention was prepared from the following ingredients:

	% by Weight	Amount
Oil Phase		
1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine	1.0	3.00 g
Isostearic acid	5.0	15.0 g
White petrolatum	15.0	45.0 g
Light mineral oil	12.8	38.4 g
Aluminum stearate	8.0	24.0 g
Cetyl alcohol	4.0	12.0 g
Witconol TM 14[a]	3.0	9.00 g
Acetylated lanolin	1.0	3.0 g
Propylparaben	0.063	0.19 g
Aqueous Phase		
Veegum TM K[b]	1.0	3.0 g
Methylparaben	0.12	0.36 g
Purified water	49.017	147.05 g

[a]Witconol TM 14 (polyglyceryl-4 oleate) is available from Witco Chemical Corp. Organics Division
[b]Veegum TM K (colloidal magnesium aluminum silicate) is available from R. T. Vanderbilt Company Inc.

The materials listed above were combined according to the following procedure:

The 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and theisostearic acid were weighed into a glass jar and heated with occasional stirring until the amine was dissolved (the temperature reached 68° C.). To this solution was added, the petrolatum, mineral oil, aluminum stearate, cetyl alcohol, Witconol TM 14, acetylated lanoline and propylparaben. The mixture was heated to 75° C. In a separate beaker, the methylparaben and water were combined and heated until the paraben dissolved (the temperature reached 61° C.). The Veegum TM K was added to the aqueous solution and heated at 75° C. for 30 minutes while mixing with a homogenizer. With both phases at 75° C., the aqueous phase was slowly added to the oil phase while mixing with a homogenizer. Mixing was continued for 30 minutes while maintaining a temperature to about 80° C. The jar was then capped and the formulation was allowed to cool.

EXAMPLE 11

An ointment according to the present invention was prepared from the following ingredients:

	% by Weight	Amount
1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine	1.0	0.20 g
Isostearic acid	5.0	1.00 g
Mineral oil	12.8	2.56 g
White petrolatum	65.2	13.04 g
Cetyl alcohol	4.0	0.80 g
Acetylated lanolin	1.0	0.20 g
Witconol TM 14	3.0	0.60 g
Aluminum stearate	8.0	1.60 g

The materials listed above were combined according to following procedure:

The 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and the isostearic acid were placed in a glass jar and heated with stirring until the amine was dissolved. The remaining ingredients were added and the resulting mixture was heated to 65° C. and then mixed while being allowed to cool to room temperature.

EXAMPLE 12

Using the general procedure of Example 11 an ointment containing the following ingredients was prepared.

	% by Weight	Amount
1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine	1.0	0.20 g
Isostearic acid	6.0	1.20 g
Polyethylene Glycol 400	55.8	11.16 g
Polyethylene Glycol 3350	32.6	6.52 g
Stearyl alcohol	4.6	0.92 g

EXAMPLES 13–15

Creams of the present invention were prepared using the ingredients shown in Table 3. The Example 1 except that benzyl alcohol was used with the isostearic acid to dissolve the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine.

TABLE 3

	Example 13	14	15
	% by Weight		
Oil Phase			

TABLE 3-continued

	Example 13	14	15
	% by Weight		
1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine	5.0	5.0	4.85
Isostearic acid	25.0	25.0	24.3
Benzyl alcohol	2.0	2.0	1.94
Cetyl alcohol	2.2	2.2	1.16
Stearyl alcohol	3.1	3.1	1.75
Petrolatum	3.0	—	2.91
Polysorbate 60	3.4	3.4	4.13
Sorbitan monostearate	0.6	0.6	0.73
Stearic acid	—	—	9.71
Aqueous Phase			
Glycerin	2.0	2.0	1.94
Methylparaben	0.2	0.2	0.19
Propylparaben	0.02	0.02	0.02
Purified water	53.48	56.48	46.39

EXAMPLE 16

A cream according to the present invention was prepared from the following ingredients:

	% by Weight	Amount
Oil Phase		
1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine	4.0	0.80 g
Isostearic acid	20.0	4.00 g
Benzyl alcohol	2.0	0.40 g
Cetyl alcohol	2.2	0.49 g
Stearyl alcohol	3.1	0.62 g
Polysorbate 60	3.4	0.68 g
Sorbitan monostearate	0.6	0.12 g
Aqueous Phase		
1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine	1.0	0.2 g
Glycerin	2.0	0.4 g
85% Lactic acid	1.0	0.22 g
Methylparaben	0.2	0.04 g
Propylparaben	0.02	0.004 g
Purified water	60.48	12.0 g

The materials listed above were combined according to the following procedure:

The isostearic acid and 0.8 g of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine were combined in a glass jar and heated with stirring until the amine had dissolved. The remaining oil phase ingredients were added to this solution and the mixture was heated to about 70° C. The aqueous phase ingredients were weighed into a separate beaker and heated with stirring until the amine and the parabens had dissolved. With both phases at about 70° C., the water phase was added to the oil phase and mixed with a propeller until the mixture cooled to room temperature.

EXAMPLE 17

The formulations of Examples 1–16 of the invention were tested in the hairless mouse skin model described above. The results are summarized in Table 4.

TABLE 4

Formulation	Number of Determinations	Average % Penetration in 24 Hours
Example 1	8[a]	21.1 ± 7.2
Example 2	16[a]	14.7 ± 4.2
Example 3	4	19.5 ± 3.9
Example 4	12[a]	14.3 ± 3.6
Example 5	4	17.2 ± 2.0
Example 6	4	36.8 ± 4.3
Example 7	4	37.5 ± 13.1
Example 8	4	18.8 ± 2.0
Example 9	4	22.4 ± 4.8
Example 10	8[a]	32.7 ± 4.1
Example 11	4	21.6 ± 1.4
Example 12	4	14.3 ± 0.6
Example 13	4	58.6 ± 9.2
Example 14	8[a]	39.6 ± 7.4
Example 15	4	28.9 ± 4.2
Example 16	8[a]	33.0 ± 9.6

[a]The determinations were run on different days in groups of 4.

As shown above, the formulations of the invention provide for significant penetration of the active agent.

Several formulations of the present invention were tested in the guinea pig model described above. The results are shown in Table 5.

TABLE 5

Formulation	Percent Lesion Inhibition	Interferon level (activity/ml)
Example 1	95	>12,800
Example 2[a]	43	1,333
Example 2	40	5,066
Example 6	29	2,133
Example 10	30	1,866
Example 13	60	1,200
Example 16	50	5,800

[a]The formulation of Example 2 was tested on two separate occasions.

The formulation of Example 1 was again run in the intravaginal guinea pig model. The protocol was as described above except that the animals were treated twice daily for 4 days starting 6 hours after infection. The results are summarized in Table 6.

TABLE 6

Formulation	Percent Lesion Inhibition	Interferon Level (activity/ml)
Example 1	71	1200

EXAMPLE 18

A mixture of 5.9415 g of the 93:7 isooctyl acrylate:acrylamide adhesive copolymer prepared in PREPARATIVE METHOD 2 above, 1.5126 g isostearic acid, 2.0075 g ethyl oleate, 0.3021 g glyceryl monolaurate, 0.2936 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine (micronized) and 23.7 g of 90:10 ethyl acetate:methanol was placed in a small glass jar. The jar was placed on a horizontal shaker and shaken at room temperature for about 13 hours. The formulation was coated at a thickness of 20 mils onto a 5 mil Daubert 164Z liner. The laminate was oven dried for 3 minutes at 105° F., for 2 minutes at 185° F., and for 2 minutes at 210° F. The resulting adhesive coating contained 59.1 percent 93:7 isooctyl acrylate:acylamide adhesive copolymer, 15.0 percent isostearic acid, 20.0 percent ethyl oleate, 3.0 percent glyceryl monolaurate and 2.9 percent 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine. The material was then laminated with 3 mil low density polyethylene backing and die cut into 2.056 cm^2 patches. Penetration through hairless mouse skin was measured using the diffusion apparatus and method described above. Three independent determinations were carried out. The aver-

age penetration in 24 hours was 46.5% of the applied dose.

EXAMPLE 19 and COMPARATIVE EXAMPLE 20

Using the method described in Example 18, the formulations shown below were prepared and the penetration through hairless mouse skin measured. The adhesive used was a copolymer of isooctyl acrylate:acrylic acid (94:6) and had an inherent viscosity of 1.45–1.60 dl/g in ethyl acetate. The solvent used was heptane:isopropanol (70:30). Patches that measured 2.056 cm^2 were employed. Three independent determinations were carried out and the results were averaged.

Formulation	Average Percent Penetration in 24 hours
Example 19	
3.0% 1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine (micronized) 15% Isostearic acid 82% adhesive	20.5 ± 6.4
Comparative Example 20	
3.1% 1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine (micronized) 96.9% adhesive	4.0 ± 1.5

This example shows that a pressure-sensitive adhesive coated sheet material of the invention exhibits superior penetration of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine as compared to one not containing a fatty acid.

EXAMPLES 21–45

Using the method described in Example 18, the formulations shown in Table 7 below were prepared and the penetration through hairless mouse skin was measured. The adhesive used was the copolymer of isooctyl acrylate:acrylamide (93:7), prepared in PREPARATIVE METHOD 1 above. The solvent was 90:10 ethyl acetate:methanol. The 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine used was micronized. All formulations were mixed at room temperature unless otherwise indicated. Patches that measured 2.056 cm^2 were used and four independent determinations were carried out for each formulation unless otherwise indicated and the results were averaged.

TABLE 7

EXAMPLE	ADHESIVE	AMINE	% By Weight ISO	OLEIC	EO	GML	OTHER	HMS
21	82.1	2.9	15.0					22.5[e] ± 1.76
22[a]	78.8	3.0	15.0			3.2		32.4 ± 1.44
23[a]	72.0	3.0	15.0		10.0			33.8 ± 2.62
24[a]	75.5	3.0	15.0		5.0	1.5		33.3 ± 2.17
25[a]	71.9	3.0		51.9	10.0			39.9 ± 5.73
26[a]	76.9	3.0		20.1				42.2 ± 1.68
27	68.3	3.0	6.0	9.1	12.1	1.5		33.8 ± 5.38
28	69.7	3.0	6.0	9.1	12.1			26.5 ± 2.61
29	70.0	3.0	6.0	13.0	8.0			44.3 ± 7.69
30	66.9	3.0		20.0	10.0			33.2 ± 7.78
31	72.0	3.0	15.0				10.0[c]	28.4 ± 3.48
32	71.9	3.0		15.0			10.1[d]	33.3 ± 2.90
33	65.2	3.0	6.0	13.1	8.1	1.5	3.1[b]	46.3 ± 3.44
34	65.4	3.0	9.0	18.0		1.6	3.0[b]	74.5 ± 3.10
35	64.0	3.0	10.0	20.0		1.6	1.5[b]	81.4 ± 5.36
36	63.9	3.0	30.0			1.5	1.6[b]	75.3 ± 5.21
37	63.8	3.0		30.1		1.5	1.5[b]	80.6 ± 5.41
38	60.1	3.1	10.0	19.8	5.5	1.5		89.3 ± 4.97
39	58.7	3.0	10.1	19.8	5.8	1.6	1.0[b]	88.0 ± 0.29
40	61.9	3.0	10.0	20.0	5.0			69.0 ± 3.00
41	60.2	3.0	10.3	20.0	5.0		1.5[b]	80.0 ± 1.24
42	58.8	3.5	10.1	20.0	5.1	1.5	1.0[b]	86.0 ± 0.78
43	58.3	4.0	10.2	20.2	5.0	1.5	1.0[b]	84.0 ± 2.01
44	57.5	4.5	9.9	20.0	5.4	1.5	1.1[b]	84.0 ± 3.61
45	57.3	5.1	10.1	20.0	5.0	1.5	1.0[b]	87.0 ± 7.23

AMINE = 1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine
ISO = Isostearic acid
OLEIC = Oleic acid
EO = Ethyl oleate
GML = Glyceryl monolaurate (available from Lauricidin, Inc., Monroe, Michigan, under the trade designation Lauricidin.
HMS = % Penetration in 24 hours in hairless mouse skin model
[a]Horizontal shaker placed in 40° C. constant temperature room
[b]N,N-Dimethyldodecylamine-N-oxide
[c]Isopropyl myristrate
[d]Diisopropyl adipate
[e]Used 3 independent determinations

EXAMPLES 46–48

Pressure-Sensitive Adhesive Coated Sheet Materials Prepared Using Unmicronized 1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine

Using the general method of Example 18 the formulations shown below were prepared. 1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine that had been ground with a mortar and pestle was used. The adhesive was the 93:7 isooctyl acrylate:acrylamide copolymer prepared in PREPARATIVE METHOD 1 above. The solvent was 90:10 ethyl acetate:methanol. All formulations were mixed at room temperature.

	Example 46	47	48
1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine	5.0	3.0	3.0
Ethyl oleate	5.1	5.0	8.0
Isostearic acid	10.0	10.0	6.0
Oleic acid	20.0	20.0	13.0
Glyceryl monolaurate	1.5	1.5	1.5
N,N-dimethyldodecylamine-N-oxide	1.0	1.1	3.0

-continued

	Example		
	46	47	48
Adhesive	57.4	59.3	65.4

The formulations of Examples 46, 47 and 48 were tested in the hairless mouse skin model (4 independent determinations per formulation) and the guinea pig model. Unless otherwise stated, patches that measured 2.056 cm^2 were employed The cream of Example 1 was run side-by-side with the patches in the guinea pig model. The results are summarized in Table 8.

TABLE 8

Formulation	% Penetration in 24 hrs	% Lesion Inhibition	Interferon Level (activity/ml)
Example 46	36.6 ± 0.88	14	700
		86[a]	4533[a]
Example 47	39.8 ± 1.44	79	2266
Example 48	30.8 ± 0.88	93[a]	>6400[a]
Example 1		93	>6400

[a]Patches measuring 3.88 cm^2 were employed.

EXAMPLES 49–51

Examples Showing the Effect of Particle Size

Using the general method of Example 18 the formulations shown below, containing 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine of different particle size, were prepared and their penetration through hairless mouse skin was measured. The adhesive used was 93:7 isooctyl acrylate:acrylamide copolymer, prepared in PREPARATIVE METHOD 1 above, the solvent used was 90:10 ethyl acetate:methanol, and the formulations were shaken at 40° C. for 72 hours in their preparation. Patches measuring 2.056 cm^2 were employed and 4 independent determinations were carried out for each formulation.

	Example		
	49[a]	50[b]	51[c]
1-Isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine	5.0	5.0	5.0
Ethyl oleate	5.0	5.2	5.1
Isostearic acid	10.1	9.9	10.1
Oleic acid	20.0	20.0	20.0
Glyceryl monolaurate	1.5	1.5	1.5
N,N-Dimethyldodecyl amine N-oxide	1.0	1.0	1.0
Adhesive	57.4	57.3	57.4
% Penetration in 24 hrs	40.5 ± 1.99	20.1 ± 0.79	67.0 ± 1.33

[a]Average particle size of 26.8 microns
[b]Average particle size of 32.9 microns
[c]Average particle size of 1.7 microns

EXAMPLE 52

A formulation with the same components in the same proportions as Example 49 was prepared using a different method. The 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine was combined with the oleic and isostearic acids and shaken at 40° C. until there was complete dissolution of the 1-isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine. The remaining ingredients were added and shaken a 40° C. for 72 hours. Patches measuring 2.056 cm^2 were prepared by the general method of Example 18. Three independent determinations were carried out, and the average penetration in 24 hours was found to be 69.7±1.24 percent of the applied dose.

EXAMPLE 53

A mixture of 2.4734 g 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine 3.3315 g isostearic acid and 6.6763 g oleic acid was prepared. To 1.8738 g of the above mixture was added 2.8750 g of the 93:7 isooctyl acrylate:acryamide adhesive copolymer prepared in PREPARATIVE METHOD 2 above, 0.2548 g of ethyl oleate, 0.0510 g N,N-dimethyl-dodecylamine-N-oxide, 0.0820 g glyceryl monolaurate (from Lauricidin, Inc.) and 14.0457 g of 90:10 ethyl acetate/methanol. The above was shaken for 30 hours at room temperature on a horizontal shaker. Transdermal patches were then prepared generally according to the procedures of Example 18.

What is claimed is:

1. A substantially non-irritating pharmaceutical formulation for topical and/or transdermal administration of the agent 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which formulation comprises:

(a) a therapeutically effective amount of 1-isobutyl-1-H-imidazo[4,5-q]quinolin-4-amine; and

(b) a pharmaceutically acceptable vehicle for said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, which vehicle comprises isostearic acid in an amount of about 3 percent to about 45 percent by weight based on the total weight of said formulation, said formulation being further characterized in that, when tested according to the hairless mouse skin model the formulation provides a penetration of the agent of at least about 10 percent of the total amount of the agent contained in the formulation in 24 hours.

2. A formulation according to claim 1 wherein said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine is present in an amount of about 0.5 percent to about 9 percent by weight based on the total weight of said formulation.

3. A formulation according to claim 1 in the form of a cream, comprising an oil phase and a water phase in admixture, said oil phase comprising:

(a) said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine;

(b) said isostearic acid;

(c) one or more emollients present in a total amount of about 5 percent to about 30 percent by weight based on the total weight of said formulation; and

(d) one or more emulsifiers selected from the group consisting of a nonionic surface active agent and a trivalent cationic emulsifier and present in a total amount of about 2 percent to about 14 percent by weight based on the total weight of said formulation;

said water phase comprising water in an amount of about 45 percent to about 85 percent by weight based on the total weight of said formulation.

4. A formulation according to claim 3 wherein said isostearic acid is present in an amount of about 5 percent to about 25 percent by weight based on the total weight of said formulation.

5. A formulation according to claim 1 in the form of an ointment comprising:

(a) said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine;

(b) said isostearic acid in ana mount of about 3 percent to about 25 percent by weight based on the total weight of said formulation; and

(c) a pharmaceutically acceptable ointment base in an amount of about 60 percent to about 95 percent by

weight based on the total weight of said formulation.

6. A formulation according to claim 3 wherein said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine is present in an amount of about 1 percent to about 5 percent by weight based on the total weight of said formulation.

7. A formulation according to claim 4, comprising about 1 percent of said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, about 10 percent of said isostearic acid, about 2 percent benzyl alcohol, about 2.2 percent cetyl alcohol, about 3.1 percent stearyl alcohol, about 2.55 percent polysorbate 60, about 0.45 percent sorbitan monostearate, about 2 percent glycerin, about 0.2 percent methylparaben, about 0.02 percent propylparaben and about 76.48 percent purified water, all percentages being based on the total weight of said formulation.

8. A formulation according to claim 4, comprising about 1 percent of said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, about 10 percent of said isostearic acid, about 6 percent cetearyl alcohol, about 2.55 percent polysorbate 60, about 0.45 percent sorbitan monostearate, about 2 percent glycerin, about 0.2 percent methylparaben, about 0.02 percent propylparaben and about 77.78 percent purified water, all percentages being based on the total weight of said formulation.

9. A formulation according to claim 4, comprising about 1 percent of said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, about 10 percent of said isostearic acid about 2 percent benzyl alcohol, about 1.7 percent cetyl alcohol, about 2.3 percent stearyl alcohol, about 2.55 percent polysorbate 60, about 0.45 percent sorbitan monostearate, about 2 percent glycerin, about 0.2 percent methylparaben, about 0.02 percent propylparaben and about 77.78 percent purified water, all percentages being based on the total weight of said formulation.

10. A formulation according to claim 4, comprising about 5 percent of said 1-isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine, about 25 percent of said isostearic acid, about 2 percent benzyl alcohol, about 2.2 percent cetyl alcohol, about 3.1 percent stearyl alcohol, about 3 percent petrolatum, about 3.4 percent polysorbate 60, about 0.6 percent sorbitan monostearate, about 2 percent glycerin, about 0.2 percent methylparaben, about 0.02 percent propylparaben and about 53.48 percent purified water, all percentages being based on the total weight of said formulation.

11. A formulation according to claim 4, comprising about 1 percent of said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, about 5 percent of said isostearic acid, about 15 percent petrolatum, about 12.8 percent light mineral oil, about 8 percent aluminum stearate, about 4 percent cetyl alcohol, about 3 percent polyglyceryl-4 oleate, about 1 percent acetylated lanolin, about 0.063 percent propylparaben, about 1 percent Veegum K, about 0.12 percent methylparaben and about 49.02 percent purified water, all percentages being based on the total weight of said formulation.

12. A method of topical and/or transdermal administration of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine for treating a viral disease in a mammal, which method comprises

(1) placing a formulation according to claim 1 on the skin of a mammal; and

(2) allowing said formulation to remain in contact with the skin for a sufficient time to permit an effective amount of the 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine to penetrate the skin to achieve the antiviral effect.

13. A method of topical and/or transdermal administration of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine to induce interferon biosynthesis in a mammal, which method comprises

(1) placing a formulation according to claim 1 on the skin of a mammal; and

(2) allowing said formulation to remain in contact with the skin for a sufficient time to permit an effective amount of 1-isobutyl 1H-imidazo[4,5-c]-quinolin-4-amine to penetrate the skin to induce interferon biosynthesis.

* * * * *

EXHIBIT C

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,238,944
DATED : August 24, 1993
INVENTOR(S) : Helen J. Schultz et al.

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page, item 75, Inventors should read --Helen J. Schultz, Amit K. Mitra, and Stephen M. Berge--.

Col. 4, line 24, after "cationic" insert --emulsifiers such as aluminum stearate can be included in--.

Col. 7, line 11, "U.S. Pat. No. 24,906" should read --U.S. Patent RE 24,906--.

Col. 11, line 63, after "above" insert --was repeated this time employing 120.0 g isooctyl--.

Col. 12, line 49, after "parabens" insert --were in solution (the temperature reached 80°C). The--.

Col. 16, line 27, "Example 2" should read --Example 2[a]--.

Col. 18, Table 7, Example 30, under the heading "EO", "10.0" should read --10.1--.

Col. 20, line 64, "ana mount" should read --an amount--.

Signed and Sealed this
Ninth Day of May, 1995

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

EXHIBIT D

CERTIFICATION

I hereby certify that this is an original copy of Application for Patent Extension of U.S. Patent No. 5,238,944.

Date: April 3, 1997

Ted K. Ringsred
Registration No. 35,658

State of Minnesota)
) ss
County of Ramsey)

On this 3rd day of April, 1997, before me personally appeared the above-named Ted K. Ringsred personally known to me, and known by me to be the person described in and who executed the foregoing instrument, and who acknowledged that he executed the same as his free act and deed, on the day and year aforesaid.

MARY L. HOFF
NOTARY PUBLIC - MINNESOTA
WASHINGTON COUNTY
My Comm. Expires Jan. 31, 2000

Notary Public